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CONTENTS

ROENTGEN ASPECTS OF DISEASES OF THE COLON

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In carcinoma of the colon, the roentgen examination is the most important diagnostic procedure. Diverticulitis, ulcerating processes, polyposis, benign strictures, megacolon, and other diseases which affect the lumenal contour of the colon, although more rarely encountered, are similarly disclosed by this examination. In infectious granulomata, the location and extent of the disease is usually determined by the roentgen examination. The most frequently encountered disturbances of the colon are functional disorders, and the value of the roentgen examination, both from the standpoint of exclusion as well as from the standpoint of furnishing aids to effective treatment, is well recognized.

In the presence of amebiasis, roentgen studies are seldom indicated or helpful, except that they furnish important negative evidence in cases where the diagnosis is unusually difficult. The diagnosis of carcinoma of the rectum is made by the clinical history, digital and proctoscopic examinations. Conditions which are primarily outside the lumen of the colon, such as sarcoma or Hodgkin's disease, or metastases, may give no roentgen evidence of abnormality. This applies to all parts of the gastro-intestinal tube[1].

In advanced lesions affecting the lumenal contour of the colon, the interpretation of the roentgen findings is usually obvious. This discussion will emphasize the early roentgen findings as well as the early clinical manifestations of diseases of the colon wherein the roentgen examination is important, in the hope that in the future, the roentgenologist will make examinations earlier in the course of the disease.

The earliest roentgen evidence of abnormal anatomical change in the colon is revealed by the careful fluoroscopic observation of the opaque enema as it enters each segment of the colon, using palpatory manipulation to separate the redundant loops as well as to detect early induration, together with the use of the double contrast method of Fischer[2,3], as modified by Weber[4], in which air or gas insufflation is employed after the expulsion of the opaque enema.

However, the customary fluoroscopic and film examinations alone are usually sufficient, provided observations *after the expulsion of the enema* are included. At this time sufficient barium will have adhered to the mucosa to permit visualization of early changes in the mucosal pattern and confusing redundancies will have disappeared because of the contraction of both the longitudinal and circular musculature of the colon. Films which are made after the expulsion of the barium enema will often give more information relative to an early lesion than those made when

the colon is completely distended with the opaque medium, but films made at both stages of the examination should routinely be made, because each stage supplements the other. If the findings are indeterminate when these examinations are completed, the double contrast method may be used.

The double contrast method involves unusual attention to details. Following the expulsion of the barium enema, if considerable barium has regurgitated through the ileocecal valve into the small intestine, or too much barium remains in the colon, the examination should be delayed a few hours until fluoroscopic observation shows only a small amount of barium in the colon. The patient has little or no discomfort if the air or gas enters the rectum slowly and evenly. We use two graduated bottles, one filled with water and elevated three feet while the other is placed on the fluoroscopic table. While water runs through rubber tubing from the upper to the lower bottle, air is displaced in the latter which passes through rubber tubing and the rectal tip to distend the colon. This is done under fluoroscopic control while the patient rotates into the most advantageous positions. The quantity of air injected can be determined at any time by observing the fluid level in the upper bottle. Stereoptican films are made after there is sufficient air or gas insufflation to furnish contrast between a lesion which may project into the lumen and the lumenal contour itself. These are visualized by the adherence of the barium to the mucosal surfaces. Later, if the patient should have difficulty in expelling the air, the reclining position and side to side rotation with the hips elevated will prove useful.

Preparation for the roentgen examination is usually satisfactory when vegetables and fruit are withheld from the diet for the day preceding, together with cleansing enemas two hours prior to the examination. If an early non-obstructing lesion is suspected, an important additional procedure is the use of two ounces of castor oil given by mouth twenty-four hours prior to the examination. This may preclude difficulty in differentiating between inspissated fecal material and polypoid lesions, especially if pedunculated. If there is clinical evidence of an obstructing lesion, when preliminary catharsis is contraindicated, a plain film of the abdomen alone may furnish sufficient evidence for localization of the lesion.

Carcinoma

Metastases from carcinoma of the colon occur relatively late in the course of the disease and, therefore this condition should be curable. The problem is to get the patient to the roentgenologist earlier in the course of the disease. Surgeons are still encountering inoperable lesions. This may be due to delay on the part of the patient, to the insidious nature of the disease, or to delay on the part of the clinician in requesting

a roentgen examination. Emphasis should be placed on the early clinical features as well as on the early roentgen evidence of the disease.

The most significant early symptom which calls for a roentgen examination is an unexplainable change in bowel habits, particularly if an unusual attack of diarrhea, although slight, has been present. The patient's knowledge of blood in the stools is often a late symptom. An unexplained secondary anemia, even though no gastro-intestinal symptoms are present, should direct attention to the right colon, as well as to the pars media of the stomach. However, the blood count may be normal and there may be no palpable mass. Pain is usually absent in the early stage of the disease. If present, pain is frequently indefinite and misleading because it occurs at a distance from the lesion. Symptoms of obstruction, regardless of degree, will, of course, suggest the presence of carcinoma.

In considering the early gross pathologic changes, it is well to remember that the lesion starts in the mucous membrane as an adenocarcinoma. Although the growth then predominantly infiltrates the wall of the colon, there is also some intralumenal projection of epithelial elements, particularly at the margins of the growth where irregular ridges are formed. This process then spreads in a circular fashion as well as longitudinally. Ulceration occurs, so that the lumen becomes irregular as well as narrower.

The early lesions are encountered more often in the left half of the colon because patients usually come to the physician earlier in the course of the disease because of symptoms of obstruction. The smaller size of the lumen, the thicker wall, and the fact that the fecal current is in a more solid state in this portion of the colon result in relatively early symptoms. A lesion which would involve only a part of the circumference of the right colon would completely encircle the left colon, producing an annular lesion. In the right half of the colon, where the lumen is large, the wall thin, and the fecal current in a liquid state, obstructive symptoms occur very late, if at all. In addition to the diffuse infiltration in the bowel wall, sufficient time will have elapsed so that often a fungating, cauliflower-like mass which projects into the lumen may exist before the patient is aware of its presence.

Therefore, in the roentgen examination, unusual care is needed in visualizing an early lesion in the *left* colon. (Fig. 1.) During the initial fluoroscopic examination, the head of the barium stream must be observed closely, while the patient is constantly rotating in the most favorable positions and the examiner separates one loop of the colon from another. At the same time, any questionable area is palpated for evidence of induration or mass formation. In the presence of an early lesion, only slight narrowing of the lumen where the marginal ridges

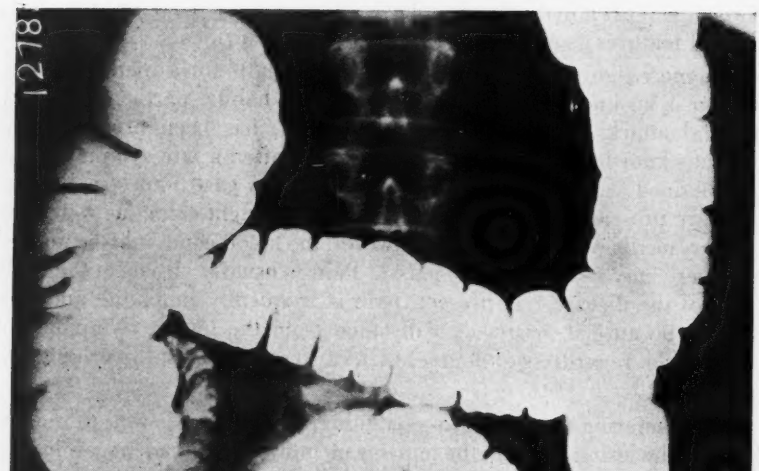

FIGURE 1.—Early adenocarcinoma of sigmoid colon. Note the short segment involved and the sharp demarcation between the normal and abnormal bowel wall. The patient had had two or three small hemorrhages from the rectum, but the blood counts were normal. Resection and end-to-end anastomosis was performed four years ago. The patient is now feeling entirely well and there is no evidence of recurrence.

of the growth project into the lumen together with some evidence of induration by palpation, may be observed.

As soon as any evidence of neoplasm is observed during the initial fluoroscopic examination, the flow of the barium stream should be stopped and films made both before and after the enema is expelled.

If the findings are still indeterminate during the subsequent fluoroscopic examination, the double contrast method should be used.

Later in the course of the disease, a definite circular filling defect (subtraction from lumenal contour where the growth projects into the lumen), together with an eccentric irregular channel and evidence of more induration, will be present. This finding is usually termed the "napkin ring" deformity. A mass, palpable under the fluoroscope, corresponding to the filling defect may not be present at the time of the examination unless the disease has progressed to the stage of definite obstruction. Under such circumstances, only the lower border of the lesion may be visualized by the use of the barium enema, and the mass may represent inspissated fecal material proximal to the lesion. Dilatation of the colon proximal, as well as distal, to the lesion may be observed. In all cases of carcinoma of the left colon, there usually is involvement of a comparatively short segment of the colon, together with a sharp demarcation between the normal and abnormal bowel wall. Stopping the barium enema as soon as a lesion is encountered is unusually important in the case of an obstructing lesion. If more barium is allowed to enter, acute obstruction may be caused by the barium above the lesion, to say nothing of difficulty in making satisfactory roentgenograms. A dilated redundant loop of colon may cover the involved area.

Following air or gas insufflation which is done in the absence of an obstructing lesion, the enema tip may be reinserted and the colon completely filled with the barium suspension under fluoroscopic observation, after which the usual films are made. Again, the film made after expelling the enema may show the lesion to best advantage.

The examination of the splenic and hepatic flexures may present difficulties because palpatory manipulation during the fluoroscopic examination may not be possible. Deep breathing and rotation into the most favorable positions on the part of the patient, together with the intermittent stopping and starting of the barium stream, will facilitate this part of the examination.

Examination of the right colon in the presence of a neoplasm is usually less difficult because of the gross pathologic features mentioned above. The intralumenal projection of the growth is apt to produce a more extensive irregular filling defect than that encountered in the left colon, and a definite mass corresponding to the defect is often present (Fig. 2).

Polyposis

Except in the presence of inflammation, such as ulcerative colitis, we have found polyposis of the colon to be a rare condition. It is often suspected when a patient gives a history of bleeding or obstruction, pos-

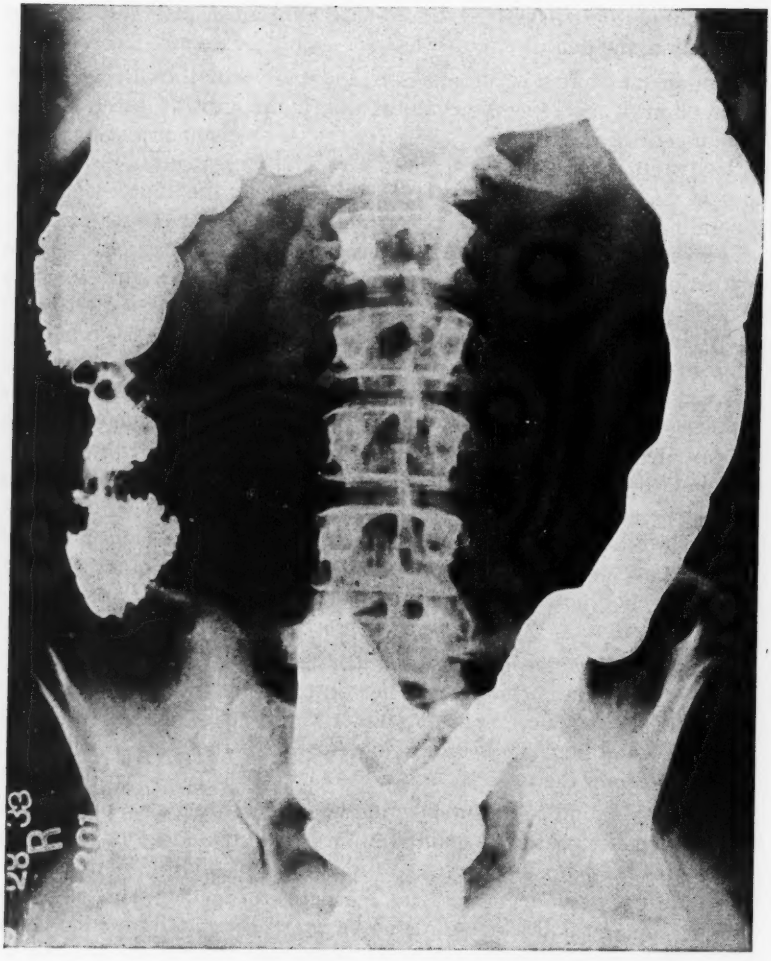

FIGURE 2.—Extensive adenocarcinoma of cecum and ascending colon. A physician, age 38, complained of weakness, loss of weight, and "some gas pains" for preceding two years. During past year, had had intravenous iron therapy. Blood count was 3,260,000 red cells with a hemoglobin of 35 per cent. At operation metastases were extensive.

sibly due to intussusception, or during the routine clinical examination, when an unexplained anemia is found. Since the presence of inspissated fecal material is the most common obstacle to accurate roentgen interpretation in this condition, it is obvious that thorough preparation of the patient is necessary before the initial barium enema is administered. The most important part of the roentgen examination is the air or gas insuffla-

tion after the expulsion of the barium enema, as emphasized by Weber[4] (Fig. 3 and 4). The roentgen features mentioned relative to the detection of an early carcinomatous lesion also apply to polyposis, for each polyp which projects into the lumen of the colon produces a filling defect. However, since there is usually little evidence of infiltration or induration of the bowel wall, there is little if any change in the lumenal contour or haustral markings. Polyposis of the colon may undergo malignant change. If surgical investigation is not made, progress roentgen studies should be employed (Fig. 8).

Diverticulosis and Diverticulitis

In a series of 3000 roentgen examinations of colons, the incidence of diverticulosis was 6.6 per cent. Diverticula of the gastro-intestinal tract are most frequently encountered in obese individuals over 50 years of age. It is difficult to determine accurately the incidence of diverticulitis because operative interference has seldom been required. The site of predilection is the sigmoid colon and a smaller number of diverticula are often found in the descending colon. Occasionally there is a diffuse diverticulosis which involves all parts of the colon, or the diverticula may be confined to the right colon. Roentgenologically, the diverticula may be visualized at one examination and not at another, depending upon the fecal content at the time of the examination.

From a pathologic standpoint, the diverticula appear first as small pits in the mucosa and submucosa; later, the mucosa herniates through the muscle layers so that little, if any, muscle tissue surrounds the extralumenal sacs. If the diverticula become infected, the inflammation may be acute or chronic with acute exacerbations, and the formation of abscesses and fistulas may constitute complications. The latter may burrow to the adjacent intestine, urinary bladder, or even to the outer surface of the body.

Diverticulitis should be suspected when the patient has the so-called symptoms and signs of left-sided appendicitis, or when a history is given of recurring attacks of intestinal obstruction associated with fever and marked tenderness, if not with a tender palpable mass in the left lower quadrant, which have recurred over a relatively long period of time. It should be noted, however, that the chief symptoms due to diverticulitis of the colon may be those of a urinary disturbance, due to extension of the process to the bladder wall.

Diverticula of the colon may be found during a routine gastro-intestinal roentgen examination following ingestion of the barium meal by mouth, together with the barium enema examination, and they are *often asymptomatic* (Fig. 5). If there is any evidence of obstruction, a plain

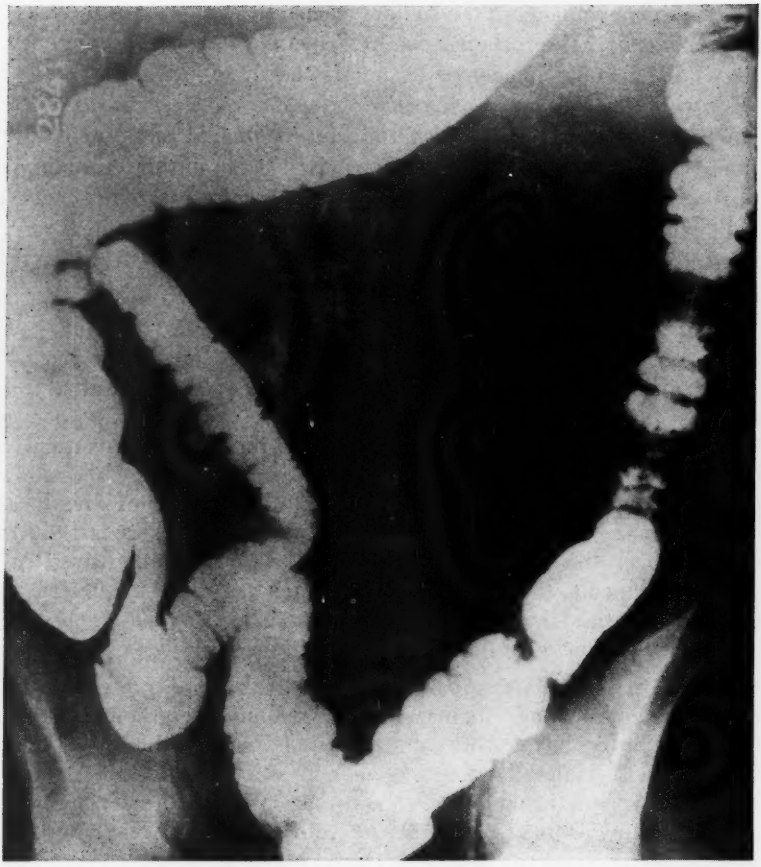

FIGURE 3.—Adenomatous polyposis of the rectum and sigmoid colon with early carcinomatous change in the rectal polypi. The usual roentgenogram taken when the colon is distended with barium suspension shows no abnormality in sigmoid colon.

film of the abdomen, followed by the barium enema examination, should be done before barium is given by mouth. If the examination is made when complete obstruction is present, in order to determine the nature of the lesion, a reëxamination may be necessary following a few days' medical management. This includes correction of body chemistry and the use of antispasmodic drugs to full physiologic effect. Even under these circumstances, the roentgen evidence may simulate that of carcinoma, but usually a longer segment of the colon is involved, characteristic serrated borders are visualized and often other diverticula are apparent (Figs. 6 and 7). In our experience, the presence of both carci-

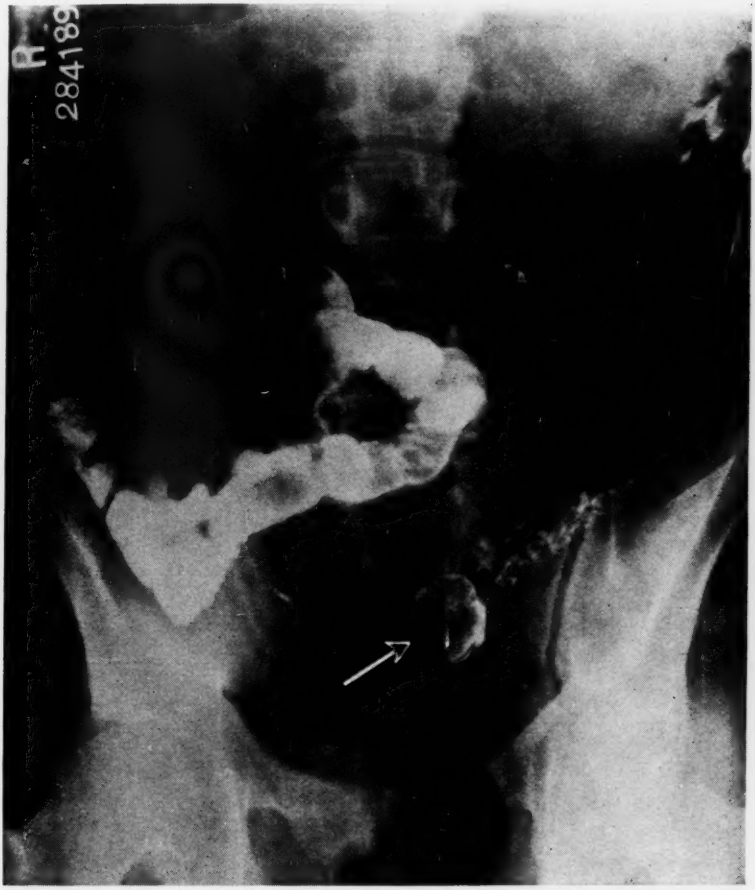

FIGURE 4.—Same case as Figure 3. Adherence of barium suspension to a large adenomatous polyp in sigmoid colon by use of the double contrast method (insufflation of air) after expulsion of the barium enema.

noma and diverticula in the same segment of the colon, although it has been observed, is a rare occurrence. If any question remains regarding the nature of the lesion, twenty-four and possibly forty-eight hour films should be made, or a reëxamination should be done in a week or ten days. Marked tenderness and a comparatively long boggy mass is often a finding revealed during the fluoroscopic examination, in addition to the roentgen findings of diverticulitis mentioned above. The proctoscopic examination usually reveals no abnormal findings because the mucosa has a normal gross appearance.

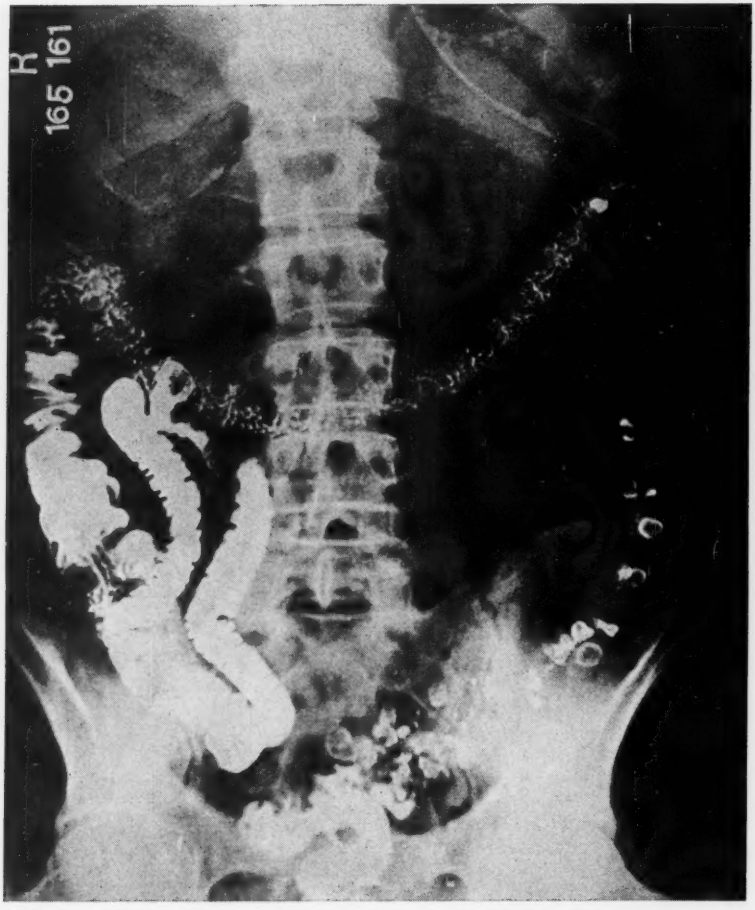

FIGURE 5.—Diverticulosis of left colon after expulsion of the barium enema.

BENIGN STRICTURE OF THE INTESTINE

Benign stricture of the intestine due to irradiation of carcinoma of the cervix uteri has been found in seven of 451 cases, an incidence of 1.5 per cent. Although this apparently is a rare condition, its presence should be suspected when a patient gives a history suggesting partial or intermittent intestinal obstruction subsequent to the original radiation therapy. This is a curable condition which may be encountered months or several years after irradiation, and its incidence, where metastatic lesions from a carcinoma of the uterine cervix are suspected, may be

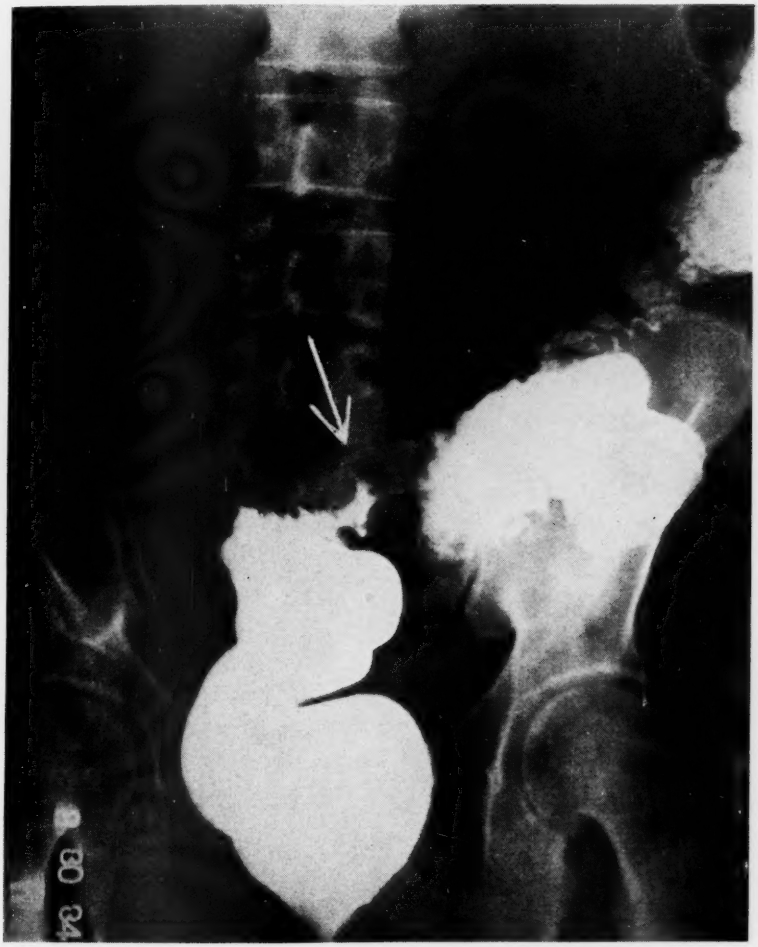

FIGURE 6.—Obstruction in sigmoid colon due to diverticulitis. Note length of segment involved, serrated channel, and dilatation of colon proximal and distal to the involved area.

greater than has heretofore been recognized. Roentgenologically, benign stricture due to this cause results in a narrow contraction of the lumen of the intestine which is most frequently found in a redundant sigmoid colon and is often fixed in position. This condition has been discussed in detail elsewhere[5].

CHRONIC ULCERATIVE COLITIS

Although the diagnosis of chronic ulcerative colitis is usually made by proctoscopic examination and examination of the stools, the roentgen

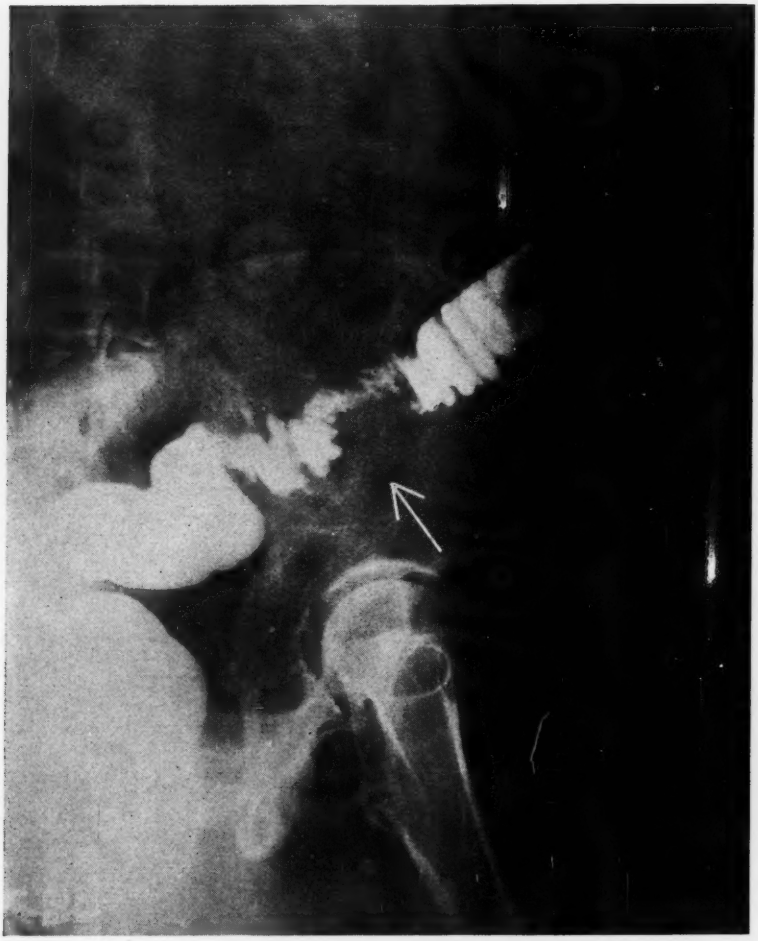

FIGURE 7.—Same case as Figure 6 one month after colostomy. Note visualization of diverticula, length of segment involved, and disappearance of dilatation of colon proximal and distal to the involved area. The colostomy was subsequently closed.

examination is often required to furnish evidence relative to the segment of the colon involved, the extent of the disease, and whether polyposis is a complication (Fig. 8). Occasionally, unsuspected ulcerative colitis is found during the course of a routine roentgen examination of the gastro-intestinal tract following the ingestion of barium by mouth.

Early in the course of the disease, the roentgen examination of the colon may show only a lack of the usual haustral markings, together

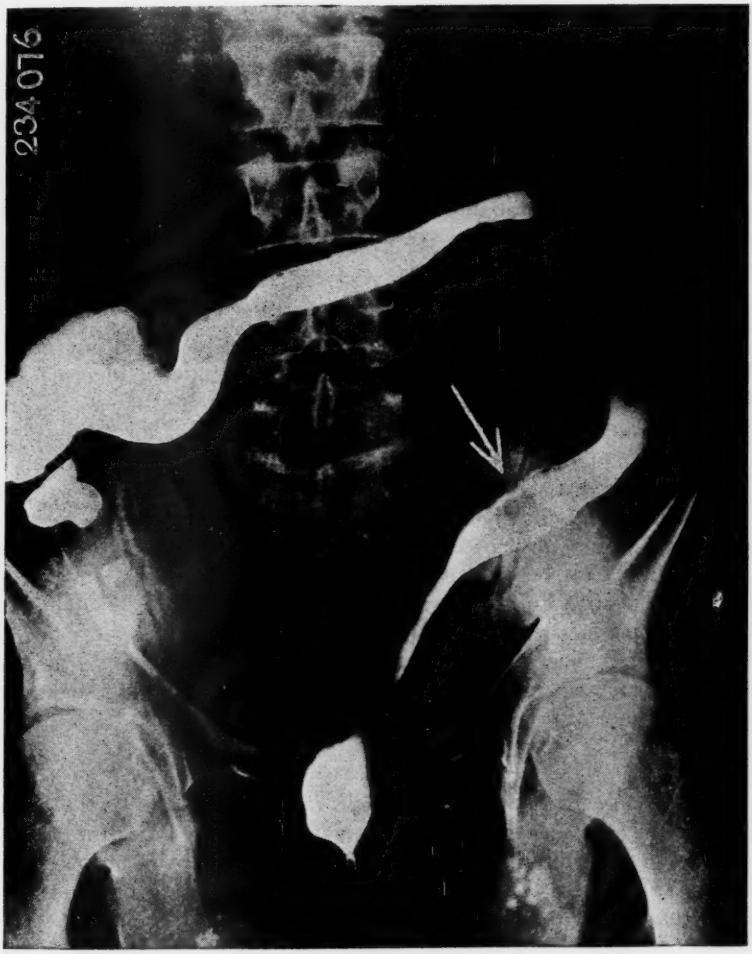

FIGURE 8.—Extensive chronic ulcerative colitis subsequent to ileostomy. Colectomy now being considered because of evidence of polyp formation in sigmoid colon which was not present during former roentgen examinations.

with unusual hypertonicity, spasticity and tenderness in the involved segment. Usually the most extensive involvement is found in the rectum, sigmoid, and lower descending colon, with gradually decreasing involvement as the cecum is approached. When there is diffuse and extensive involvement, not only is the lumen of the colon narrow, but the longitudinal axis of the colon is much shorter than the normal colon. During the fluoroscopic examination, the enema fills the colon instantly

and regurgitation occurs through the ileocecal valve. The colon may be empty by the time a film can be taken. In the involved portions, there will be a lack of haustral markings and the diameter of the lumen will be reduced to that of a narrow tube having irregular borders. Palpation during the fluoroscopic examination will reveal a rigid tender tube having thick walls. Localized chronic ulcerative colitis will present similar findings in the involved segment and may be difficult to differentiate from a neoplasm. In the former, however, a longer segment of the colon is usually involved and there are usually associated spastic phenomena which are absent from the latter.

Amebiasis

In our experience, roentgen examination is seldom helpful in the diagnosis of amebiasis, except that it furnishes negative evidence. The diagnosis is usually made by the history, examination of the stools, and the proctoscopic examination. However, Brown[6] in an analysis of 533 cases, found that only one-third of the patients with active amebic dysentery had grossly visible rectal ulcers, and only one-tenth of the patients infected with Endamoeba histolytica had ulcers in the rectum, so that the positive proctoscopic findings, although very important when present, are relatively infrequent. If repeated examinations of the stools are negative and if there has been a long duration of symptoms, the roentgen examination may be helpful. If so, there will be evidence of ulceration in the cecum and ascending colon. The location of the disease, plus negative roentgen findings in the chest, will be highly suggestive of the presence of this disease.

Tuberculosis of the Intestine

From the roentgen standpoint, the ulcerative type of intestinal tuberculosis produces changes which are characteristic of any type of ulcerating process in the intestine. Roentgen evidence of involvement of the terminal ileum and cecum, the site of predilection, in a young adult who has pulmonary tuberculosis or a primary focus elsewhere in the body, makes the diagnosis of intestinal tuberculosis highly probable. *Roentgen studies of the chest should always be made in cases where there is evidence of an ulcerative process in the right colon, even though the patient has no pulmonary symptoms or physical findings.*

The hyperplastic (tuberculoma) type often presents roentgen evidence which is difficult, if not impossible, to differentiate from a neoplasm. Tuberculoma, of course, usually occurs in younger individuals and its duration will be in terms of years rather than in months. Again the site of predilection is the cecum. Both types of intestinal tuberculosis start in the lymphoid tissue of the submucosa. In the ulcerative type, the process becomes predominantly destructive, while in tuberculoma there

is a predominant formation of granulation tissue and fibrosis. The lumenal contour which the roentgenologist visualizes will be altered accordingly. The new tissue formation in the submucosa in the hyperplastic type will gradually push the mucous membrane into the lumen in folds so that there will be nodular intralumenal projections in the form of papillomatous masses. Meanwhile, the wall of the bowel becomes thickened and stiff so that an irregular boggy mass is palpable during the fluoroscopic examination.

The work of Stierlin (1911) and of Brown and Sampson (1919) in establishing the roentgen diagnosis of ulcerative intestinal tuberculosis is well known. The Stierlin sign, that is the lack of haustral segmentation, the irregular contour of the lumen, associated with hypermotility and marked hyperirritability of the cecum (so irritable that barium, whether given by mouth or enema, may not remain in the cecum long enough for satisfactory visualization), is no longer considered pathognomonic of intestinal tuberculosis. Similar evidence is found in any ulcerating process of the intestine, but may be sufficient for diagnosis in patients who are known to have pulmonary tuberculosis. As is the case in the study of all early lesions of the colon, the barium enema and the combined double contrast method, using either air or gas insufflation after the expulsion of the enema, gives evidence of the earliest anatomic change.

Non-specific Infectious Granuloma of the Intestine

This condition which was established as a clinical entity by Crohn[7] and which has many clinical names, such as "Regional Ileitis" (Crohn) and "Regional Enteritis" (Brown[8]), is very uncommon in our experience. Jones and Byrne[9] have reported four of our cases. Crohn and Rosenak[10] have recently reported sixty cases, in nine of which there were simultaneous inflammatory changes in the colon. This experience coincides with that of other observers who have found that the condition, although most frequently found in the terminal ileum, may be primary in any part of the small intestine, and there may be associated lesions in the colon. There has been some discussion as to which is the primary site when lesions are present in both the small and large intestine. The process is different in the two locations. "Primary ileitis is a granulomatous process, thick, hard, eventually with cicatrizing involvement of the ileum, as opposed to the flat, thin, superficial ulceration of colitis with ileac involvement; the latter never goes on to granuloma or to cicatrization or stenosis" (Crohn[10]).

The preoperative clinical differentiation is usually impossible. The patient may consult the physician during the early phase of the disease when there are symptoms which simulate recurring appendicitis, even

though the appendix has been removed, or during the ulcerating enteritis phase when the disease simulates chronic ulcerative colitis, or during the third or stenotic phase, when the signs are those of partial or intermittent complete intestinal obstruction. The formation of fistula, either internally to the adjacent colon or other visera, or externally, may be the predominant feature at any stage of the disease. Roentgen examination usually reveals the location of the disease process which, in the absence of positive roentgen chest findings (to exclude tuberculosis) makes this diagnosis highly probable. If the patient is seen during the stenotic phase, a plain film of the abdomen may reveal the approximate site of the obstruction. However, since the ulcerating phase is the one most commonly encountered, the roentgenologist usually makes the barium enema examination first when the symptoms are those of chronic ulcerative colitis. When the disease is limited to the small intestine, the barium enema will show a normal colon, which is very important negative evidence. If the lesion is limited to the terminal ileum, its most frequent site, the regurgitation of the barium enema through the ileocecal valve discloses evidence of ulceration at this site and this is positive evidence. Since the disease in the small intestine is a *slowly* cicatrizing process (the duration of symptoms may be several years), the barium meal usually can be administered without fear of producing complete obstruction. By making interval studies while the barium meal passes through the small intestine, the site of the lesion is usually determined. The roentgen evidence of an inflammatory process is the same whether the lesion is in the small or large intestine, and the evidence revealed depends on the character, severity, and extent of the pathologic changes present at the time of the examination. Mucosal destruction, narrowing as well as shortening of the lumen, mural thickening as determined by palpation during the fluoroscopic examination, together with either hypermotility or evidence of obstruction with dilatation of the intestine proximal to the lesion are the most commonly observed findings. If an external fistula is present, the simultaneous injection of an opaque medium at the time of the other roentgen studies often determines the course and distribution of the fistula. Since resection of the involved segment of small intestine is curative, it is hoped that in the future the condition will be discovered earlier in the course of the disease and that, when operation in the interval between suspected recurring attacks of appendicitis is done, exploration of at least the terminal segments of the ileum will be included.

Megacolon

The diagnosis of this condition, either when a diffuse or a localized involvement of the colon is present, is easily established by the roentgen examination, by the use of the barium enema.

ROENTGEN ASPECTS OF DISEASES OF THE COLON

Functional Disturbances of the Colon

Functional gastro-intestinal disturbances with colon manifestations are the most frequent cause of chronic gastro-intestinal disability. They may simulate or may be secondary to any diseased state in the abdomen, if not elsewhere in the body. If such disturbances are primarily functional, the duration of the disability is usually longer than that in organic disease, except chronic ulcerative colitis and diverticulosis, but the possible occurrence of an organic lesion in association with the functional element must not be forgotten. Functional disturbances of the colon are most commonly due to improper bowel habits or to a hypersensitive nervous system in general, but they may be secondary to diseases elsewhere, such as a pathologic appendix or diseases in the gallbladder or urinary tract. The rôle of gastro-intestinal allergy is assuming increasing importance. There may be several causes for the disability. *Gastro-intestinal diagnosis often involves a process of exclusion.* Therefore, unless the symptoms are definitely localized to the colon, complete roentgen studies as well as other clinical studies are indicated.

As discussed elsewhere[11] our routine roentgen studies in these cases are as follows: Films of the gallbladder, kidney and urinary bladder are made first. If any abnormality is revealed in the urinary tract, the patient is then sent to the Genito-Urinary Department for examination. Intravenous urography or retrograde pyelography, if indicated, are done before the barium meal is given. This is followed by cholecystography, combined with a complete study of the gastro-intestinal tract, which includes the barium meal, fluoroscopic and film examinations of the stomach and intestine, as well as the barium enema examination of the colon. Finding an unsuspected organic lesion during a roentgen gastro-intestinal series' examination is not unusual. Therefore, the roentgenologist not only aids in determining the presence or absence of disease, but also determines the physiological activities of the gastro-intestinal tract. Motility studies may show unusual findings. The colon may be unusually irritable, regardless of the presence of unusual atonicity or spasticity. At any rate, probably the most helpful evidence in the localization of the disturbance is (1) the accurate reproduction of the patient's abdominal distress while the barium enema is administered, and (2) the relief experienced after the expulsion of the enema. *Symptoms due to disturbances in the colon may be referred to any part of the abdomen, including the epigastrium,* as demonstrated by Smith[12] and others. If evidence of an organic lesion is questionable, the roentgenologist should not hesitate to request reëxaminations after adequate preparation, just as other reëxaminations may be required in solving other clinical problems.

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TRANSURETHRAL RESECTION OF THE PROSTATE

A Five Year Review

W. J. ENGEL, M.D.

After five years' experience with transurethral resection of the prostate, it seems worth while to evaluate our results. When the method was revived with new interest about five years ago, there was much controversy regarding its merit and the advisability of its use, but the test of experience has shown that the operation has met all requirements and has won a permanent place in the surgical treatment of bladder neck obstructions. This review includes the results secured in a series of 453 transurethral resections which I have performed; 62 were done for carcinoma of the prostate and 391 for various types of benign hypertrophy.

Prostatic obstructions are of two main types: (1) malignant and (2) benign. The former is recognized by the characteristic hard, nodular, fixed prostate, often with extension up toward the seminal vesicles. The clinical history usually reveals obstructive symptoms of relatively short duration (6 months to 1 year) which have then developed fairly rapidly. Marked bladder irritability is also suggestive of this type of obstruction.

The benign hypertrophies are subdivided further according to which of the lobes predominate. Thus, we have solitary middle lobe hypertrophy, simple bilateral lobe hypertrophy, the combined bilateral and middle lobe enlargement and, in addition, the sclerotic or glandular median bars. In these benign enlargements, the clinical history is of long duration, the earliest symptoms being increased frequency with some hesitancy in starting the stream, diminished force and nocturia. These symptoms gradually increase over a period of years until complete urinary retention finally results in many cases. Rectal examination may reveal a large, smooth, rounded gland but, on the other hand, too much reliance should not be placed on rectal palpation for it is a common experience to see even complete retention due to a middle lobe hypertrophy or a bar where rectal examination has revealed a relatively small prostate gland. A careful clinical history is, I believe, a more reliable guide in the diagnosis of bladder neck obstruction.

Thus the same type of lesion is not seen in all cases of bladder neck obstruction but various types are encountered. We have always contended that all types were not suitable for resection, but as time has gone on and experience increased, more and more cases are being treated by this method until it is now felt that only the very large, bilateral lobe hypertrophies require complete prostatectomy. This is a

very small group as may be judged from the fact that during the year 1935, it was necessary to do only nine prostatectomies.

The two chief advantages of resection are that there is less risk to the patient and the morbidity is diminished.

1. Less risk to the patient. Only eight fatalities have occurred in 453 cases, a mortality rate of 1.7 per cent. Four deaths occurred in the group of 391 benign cases, a mortality of 1.5 per cent and three deaths occurred in the group of 62 carcinomas, a mortality of 4.8 per cent. Most of the fatalities occurred in the earlier cases and no deaths have occurred in the last 206 consecutive cases of all types. It must be remembered too that the whole group includes many patients who were over eighty years of age and whose general condition would have precluded any other type of surgery. No attempt has been made to select only the good risk patients for this operation.

2. Diminished morbidity. The average hospitalization was nine days, the shortest four days and the longest forty-four days. Convalescence is not prolonged and many of the patients have resumed normal activities two weeks after operation. This has a decided economic aspect in that hospital expense is reduced and the patient is able to resume his occupation earlier.

The preoperative preparation has been progressively less rigorous during the five years. Originally, we used routine preliminary catheter drainage as for prostatectomy, but all too often, we encountered the elevation of temperature on the second or third day which is so commonly seen in patients with an inlying catheter. Therefore, this practice was gradually abandoned except in the badly infected and atonic chronically overdistended bladders. We have even gone farther in many of the more recent cases by dispensing with the preliminary cystoscopic examination. After general physical examination, the patient with a typical history of urinary obstruction is admitted to the hospital without any preliminary urethral instrumentation. A blood urea determination is made and the kidney function is determined by the urea clearance test. If these show no striking variation from normal, the patient is sent to the operating room the following day, given a spinal anesthetic and all preparations are made to proceed with the operation. The resectoscope is introduced, the bladder and bladder neck surveyed with the observation telescope and, if suitable for resection, we proceed with the operation. If not suitable (a circumstance not yet encountered since managing cases in this manner) we have simply given the patient the advantage of a cystoscopic examination under anesthesia and, at a later time, prostatectomy is carried out. It is actually true that patients handled in this manner have had less reaction than is occasionally seen

following cystoscopic examination or even simple urethral catheterization. It is to be understood that this management applies only to the average uncomplicated cases which constitute, however, a considerable proportion of patients seen.

The technic of the operation need not be given here but it should be emphasized that it is not an easy operation to perform and, to one who has done both, it is decidedly a more difficult procedure than prostatectomy. The amount of tissue to be removed varies according to the individual case, but in every instance, sufficient tissue must be removed to create an unobstructed channel from the trigone of the bladder out to the verumontanum. In my experience, bleeding has not been a troublesome problem and in only one instance has it been necessary to open the bladder suprapubically because of bleeding. This occurred four years ago which was quite early in our experience with the method. Great care must be exercised to prevent injury to the external sphincter. Not a single instance of urinary incontinence has been encountered in the entire 453 cases.

Postoperatively, these patients have very little discomfort and minimum sedation is required. The catheter is removed routinely on the second day following operation and the patient is then allowed to get out of bed and to have bathroom privileges. The average patient will experience some frequency and bladder irritability for a few days but ordinarily this subsides quite rapidly. Usually the patients are dismissed from the hospital five to seven days following the operation.

The results of the operation have been eminently satisfactory when the five year period is considered. Benign hypertrophies must, of course, be separated from carcinomas of the prostate when results are discussed.

In the cases of benign hypertrophy, all patients have been relieved of their symptoms of obstruction, although a small group still have some bladder irritability and frequency. One fact stands out prominently; that is, the results of the operations performed in the past two or three years have been more uniformly satisfactory than in the earlier cases. This may quite logically be attributed to increased experience which brings greater courage to remove larger amounts of tissue. In view of more recent experience, I am now certain that in many of the earlier cases, an insufficient amount of tissue was removed to secure a perfect result. When the results with the entire group of patients with benign hypertrophy are evaluated, we find that 90 per cent have had entirely satisfactory relief from their symptoms while only 10 per cent, although relieved, still present some bladder complaints or have been found to carry some residual urine. Most of this latter group, however, are quite satisfied with the result as compared to their condition before operation.

It is with hesitancy that results have been expressed in numerical figures, and it is done only to give a general picture of the effectiveness of the operation. So many individual factors are present which affect the result that each patient should be analyzed separately to give a true picture. Such associated conditions as diverticulitis of the bladder, atony from long-standing obstruction, the degree of renal impairment and the general health and vitality of the patient have a decided bearing on results and are not taken into consideration when the group is analyzed as a whole. When one considers all these factors, it is not surprising that a small percentage of the patients continue to have some trouble even though their condition has been improved markedly. In some instances, therefore, one must be satisfied to have made a bad situation better. It must also be remembered that many patients who were extremely bad risks could not have survived prostatectomy, but these have been made comfortable by resection.

The question of recurrence is decidedly pertinent when considering results. When the method was new, one of the criticisms presented by antagonists was that the obstruction would quickly return since only a part of the gland is removed. The fact is, however, that of the 391 operations performed for benign hypertrophy, a second resection for recurrent obstruction has been necessary in only six instances and all of these occurred in the early cases in which I now believe, as previously stated, that an insufficient amount of tissue was removed at the original operation. It would seem that a five year period is sufficiently long to conclude that recurrence is decidedly infrequent and even if it does happen, the operation can safely be repeated.

In carcinoma of the prostate, resection constitutes merely an important palliative method and cannot, of course, cure the disease. Unfortunately, malignancy of the prostate produces no symptoms until urinary obstruction occurs and, by that time, it is so extensive that complete removal is not possible. One is called upon, however, to relieve the symptoms of obstruction and resection offers an ideal method.

Resection has been performed in sixty-two cases of carcinoma of the prostate and in thirty of these, radiation therapy has been added; that is, deep x-ray or radium. There were three operative deaths, a mortality of 4.8 per cent. In every instance, the obstructive symptoms were alleviated and the patient's comfort increased. In general, the patients who had radiation in combination with resection, survived longer than those in whom resection alone was done, the average survival being two years in the former as compared to one and two-thirds years in the latter. It has been necessary to perform a second resection within a year for recurrent obstructions in several of the patients with malignancy. The chief grati-

fication to be derived from the results in carcinoma of the prostate is the knowledge that the comfort of the patient has been increased and that he is not forced to endure a permanent suprapubic cystotomy, a method previously recommended for the relief of obstruction due to an inoperable prostatic malignancy.

Thus we believe as the result of this experience, that transurethral resection has proven its merit, and is the operation of choice in the vast majority of cases of bladder neck obstruction. The results have been gratifying to the patient as well as the surgeon and it has been a step forward in the management of this distressing disease of old age.

CARCINOMA OF THE CERVIX: ITS DIAGNOSIS AND TREATMENT

THOMAS E. JONES, M.D.

In spite of the numerous articles which have been written on the subject of carcinoma of the cervix as well as the educational campaign which The American Society for the Control of Cancer has sponsored, a recent review of the histories of patients whom I personally have examined and treated shows that the disease was just as far advanced in those seen in 1935 as those seen in 1920.

For many years, women refused operation for cancer of the cervix because they felt that early recurrence usually occurred following operation, so that little was to be gained by this procedure. The extensive and successful use of radium in the past 15 years should have eliminated this objection, but the laity has come to believe that the pain which accompanies the late stages of the disease is due to a radium burn and for this reason many patients refuse radium treatment. Therefore, in spite of an educational campaign to inform women of the danger of carcinoma of the cervix, and in spite of the advances in the use of radium, many patients with this condition still do not present themselves for treatment until the disease has advanced to an incurable stage.

On the other hand, it is frequently found that many of these patients with advanced carcinoma of the cervix have consulted a physician from four to six months previously, only to be assured that they had no cause for worry. Had the true nature of the condition been recognized and proper treatment instituted at that time, some hope of cure might have been given to the patient. When a patient consults her family physician because of some supposed menstrual disorder, he must assume the responsibility and convince himself by a thorough physical examination that there is or is not an existing pathologic condition, and if there is, treatment must be instituted promptly. Consultation without proper examination gives the patient a false sense of security which leads to a delay of several months and often is just the time required for a carcinoma to advance from an operable to an inoperable stage.

The controversy regarding the relative merits of surgical and radiation treatment for cancer of the cervix has been fairly well settled. It is generally agreed that surgery is excellent treatment for early cases, but these are so rarely recognized that they can almost be disregarded. On the other hand, it is quite fair to say that radiation will cure as many of the early cases as will surgery without any mortality or morbidity.

CARCINOMA OF THE CERVIX: ITS DIAGNOSIS AND TREATMENT

Etiology and Prophylaxis

The etiology of cancer of the cervix or of any other part of the body is not known, and I do not propose to discuss the various theories that have been advanced. We can only analyze as carefully as possible the conditions existing in the area in which cancer has developed. The established relationship between chronic irritation and cancer indicates that better obstetric care and surgical prophylaxis in the treatment of ulcers and tears will reduce the incidence of cancer of the cervix.

The fact that 90 per cent of all carcinomas of the cervix occur in multiparous women cannot be looked upon merely as a coincidence. There must be an etiological relationship, and it is generally believed that the basic origin is parturitional trauma with sequential cell metaplasia. This may be regarded as the most definitely known lesion to precede cervical cancer, and it may be considered as essentially the exciting or secondary cause of the disease. It has also been demonstrated conclusively that only in the most exceptional instances does carcinoma develop in damaged cervices when prompt and adequate treatment is given following childbirth. In the final analysis, cancer of the cervix is largely an expression of incomplete maternity service, and it becomes obvious that the solution of the problem rests almost wholly in the hands of the obstetrician who, in most instances, is the family physician. Therefore, the responsibility for prophylaxis of cervical cancer falls upon him more than upon any other individual. The obstetrical service is not complete unless it includes a thorough examination from six to eight weeks after parturition when, if necessary, repair or linear cauterization of the erosion may be applied to insure complete healing.

Graves studied five thousand cases in which cervical repair had been done and found that malignancy developed later in only four patients. While these figures have not been compared with another series of equal size, they furnish sufficient proof that when proper care is given to the cervix after labor, it constitutes a very effective method of prophylaxis.

Erosions, eversions and leukoplakia may also be considered as precursors of malignancy. Erosions and eversions are best treated by linear cauterization with electric cautery and usually this can be done in the office. Electrocoagulation is also an excellent procedure, and the patient is required to remain in the hospital for only a few days.

Although leukoplakia has been known for many years, it has received far too little attention as a causative factor of cancer of the cervix, and this is probably true because it is difficult to recognize the condition unless you are actually looking for it. Its appearance in the mouth and on the tongue is familiar but often it is not recognized in the vagina. It may occur as bluish, pearly or grayish white plaques

which either are level with the mucosa or slightly raised if the hyperplastic process is excessive. In the diagnosis of leukoplakia, the cervix may be painted with Lugol's solution, and the healthy tissue will take the stain while the diseased tissue will not. However, ordinarily all pathology here is visible to the naked eye if one knows what he is looking for.

Diagnosis

When pain, hemorrhage and an odorous discharge are symptoms of carcinoma of the cervix, they usually indicate that the growth has advanced to an incurable stage; therefore, the condition must be recognized before these symptoms appear. The cause of any deviation from the normal menstrual cycle and of any vaginal discharge must be determined. The fact that any discharge is pathologic and the simplicity of the equipment for pelvic examination, as well as the easy accessibility of the cervix for inspection, all should render the diagnosis of carcinoma of the cervix a very simple matter for every physician. In case of any doubt regarding the diagnosis, biopsy may be done and we feel certain that it does no harm.

Some time ago, many articles appeared in the literature on the dangers of biopsy and the general feeling expressed by them was that distant metastases would result. On the other hand, dilatation and curettage were recommended for diagnostic purposes—what is the difference? Distant metastases from cancer of the cervix rarely occur, and in practically all patients who die from the disease, it is found that carcinoma is confined to the pelvis. The caution regarding biopsy may have discouraged physicians from employing this diagnostic procedure and may account in a large measure for some of the delay in diagnosis. Biopsy is not a major procedure, and it can be done in the office with small biting forceps. Less harm will be done by biopsy than by waiting for three or more months just to see how things will turn out. *Take biopsies freely from any suspicious areas.*

Rationale and Technic of Radium Therapy

The simple idea that radiation is a means of destroying cancer cells without too much injury to the normal cells is a good working hypothesis, but our accumulating knowledge regarding the physics and biologic effects of radiation has led to a better understanding of its action. In brief, radium has a threefold action on malignant tissues. It affects (1) the cancer cells, (2) the connective tissue and (3) the blood and lymph vessels. The action on the cancer cell is shown microscopically by swelling and vacuolization of the protoplasm and by shrinking of the nucleus. This is followed by phagocytosis and absorption and re-

placement by a homogenous connective tissue. This contracts and affects the lymphatic and smaller blood vessels and starves the growth.

Many varieties of technic have been used since radium therapy was instituted and many men have contributed to the advancement of our present knowledge, but there still remain two entirely different schools of thought in regard to the method of treatment. In one, the opinion is that it is best to give large massive doses in a short period of time, preferably in one or at most, two sittings. The other school believes that it is preferable to give very small doses over a long period of time. This difference of opinion undoubtedly will be settled before many years after the results of both methods are compared, but I believe that at the present time, most of the workers in this country favor the former opinion. Standardization of radium dosage for uterine cancer is impractical and dosage and technic must vary with the character and location of the involvement. At the Cleveland Clinic, we have altered our technic very little during the past 10 years, the only change being that since a larger amount of radium has been available, larger doses are given over shorter periods of time. We try to give the complete dose at one sitting, whereas previously the total amount of radiation was given in two doses. The average dose in our earlier cases was 4200 mg. hours distributed evenly in and against the cervix. In our later cases, since we have combined radium with high voltage x-ray, the average dose is about 3600 mg. hours. Our standard screen is made of brass, one and one-half mm. in thickness and this is encased in a rubber tube 3 mm. thick. At the present time, we place a tube in the fundus as well as in the cervix because in our earlier cases, we found that frequently a patient may be free from symptoms for a year or so and then suddenly have bleeding and discharge. Examination would then reveal a large undermined cavity at the upper end of the vagina which was the result of not placing the radium high enough in the cervical canal. Because of this finding, we believe that an anesthetic is necessary in order to estimate the extent of the growth and also to facilitate the accurate placement of the radium in proximity to the growth. It is sometimes impossible, even when the patient is under an anesthetic, to insert a tube of radium high in the cervical canal.

In addition to the radium tubes in the fundus and cervix, two or three tubes are placed against the cervix and these are held in position by packing the vagina tightly with gauze. If the growth is of the cauliflower variety, it is frequently curetted away or radium needles are placed in it. A catheter is then introduced into the bladder to keep it empty and, therefore, as far away as possible from the radium. Care should be taken in transferring the patient from the table to the cart and from the cart to the bed. We believe that bending and twisting the

patient during transfer will dislocate the vaginal tube and may account for bladder and rectal symptoms. The best method is to place the cart beside the table and slide the patient on the cart by means of a sheet and from the cart to the bed in the same manner, so that the position of the patient is unchanged throughout the procedure.

We have not used gold seeds in the treatment of any of these primary growths, but they are of great value in the treatment of recurrences because their action is more or less localized. Large, heavily filtered doses frequently are harmful in the treatment of recurrence. We have not had any experience with placing gold seeds in the broad ligaments by laparotomy.

The majority of the patients are able to leave the hospital the day following treatment unless they live some distance away. They are instructed not to be too active and to take a douche once or twice daily. An appointment is given for return in three or four weeks for high voltage radiation therapy which is administered by Dr. Portmann. The treatment is given in four or five doses over a period of four or five days. After patients have been treated, we make an effort to have them return at monthly intervals for three months and after that every three months during the following year. If local recurrences develop, they are treated with radon seed implantation. If the recurrence is deep, radiation therapy is repeated with marked relief for a time. In cases in which there is no ureteral involvement but pain is referred down the legs, we perform a chordotomy, a bilateral lumbar sympathectomy, just as a gasserian ganglion operation is done for relief of pain in cases of extensive malignant disease of the face.

We believe that surgery following apparent cure by radium therapy is not only unnecessary but is frequently disastrous, and many surgeons who employed this procedure from five to ten years ago have now abandoned it. Neither should radiation be relied upon to offset the disaster of an incomplete operation.

Complications

The chief complications of the treatment of carcinoma of the cervix by radium are the production of symptoms referable to the rectum and bladder and of urinary and fecal fistulae. Symptoms of bladder and rectal disturbances are of two types—early and late, and it is quite important that they should be recognized. It is reasonable to assume that if a sufficient dose of radium is given to cure carcinoma of the cervix, it will also be sufficient to produce an erythema to the rectum or bladder. Very often, this erythema is slight and passes unnoticed unless the patient is questioned. If it is severe, it is evidenced by a

slight burning sensation and a desire to go to stool or to void somewhat more frequently than usual. In the mild cases, the condition usually clears up in from ten days to two weeks, but in the severe cases from four to six weeks may be required. In this latter group of cases, the late rectal and bladder complications usually develop six or eight months after the initial radiation treatment. These late symptoms are often mistaken for recurrence of the carcinoma, and if the patient is treated for recurrence, irreparable damage will result. A clue to the true state of affairs is found in the fact that the symptoms are entirely out of proportion to the findings. There are severe pains and tenesmus, and the stool contains considerable blood and mucus. Digital examination causes greater pain than is produced when recurrence is present. The patient is not cachectic. Proctoscopic examination reveals a puckered-up scar or small ulcer at about the level of the cervix with telangiectasis and considerable redness of the mucosa. The condition may be compared to an overtreated area on the skin which has healed by the formation of scar tissue through which fine vessels may be seen. In the rectum, the scarring is subject to trauma and infection from subsequent ulceration which causes the late symptoms.

When bladder symptoms are present, cystoscopic examination reveals an area of intense redness and sometimes of ulceration. Occasionally, urinary salts are deposited in the slough in the bladder, and stones will be formed.

Treatment of the rectal symptoms consists of rest in bed, cleanliness of the lower bowel and the injection of three or four ounces of warm olive oil into the rectum twice a day. Occasionally, an opium suppository is necessary.

Irrigation of the bladder and the instillation of gomenol are recommended for treatment of the bladder symptoms. From four to six months may be required for the treatment of these bladder and rectal complications, but the cases in which these symptoms occur comprise a very small percentage of the total number.

Another complication is a rather new clinical entity which is called benign stricture of the intestine following radiation therapy. This may develop and surgical intervention may be necessary many months or even years after complete regression of or cure of the cervical cancer. The importance of recognizing this complication is perfectly obvious, because the pain due to the obstruction is easily construed as or confused with that produced by metastatic carcinoma. In a series of 451 cases of cervical carcinoma which have been treated by radiation therapy up to July, 1934, seven known cases of benign stricture of the intestine causing obstruction have been observed. In five of these cases, the stricture was in a movable segment of the sigmoid and in two cases in

the small intestine. All of these were observed in patients who had received irradiation for cancer of the cervix, but the increasing use of the radiation for other conditions necessitating exposure of the intestine may result in similar complications. The time of onset of the obstructive symptoms in these cases varied from eight months to eight years, and in no case was there any evidence of malignancy in the pelvis or in the stricture.

The rate of recurrence of cancer is so high that almost any abdominal or pelvic pain may quite naturally and logically be attributed to malignant extension or malignancy. If the condition is actually benign and is caused by radiation therapy, it is quite obvious that additional radiation treatment would aggravate this condition. Before attributing this disability to metastases, thorough pelvic and sigmoidoscopic examination should be made, and this should be followed by roentgen examination of the gastro-intestinal tract if necessary. We know from experience that carcinoma of the cervix generally remains confined to the pelvis, so that if the pelvis is free from induration and the patient has a pain simulating obstruction, exploratory operation is justifiable before the patient is referred for roentgenotherapy which may prove disastrous. In our series, five patients were restored to normal health by resection or short-circuiting operations.

Summary

The incidence of carcinoma of the cervix is not decreasing in spite of improvement in diagnostic and therapeutic procedures and in spite of the efforts of various organizations to inform the laity of the importance of early diagnosis and treatment.

In addition to conditions resulting from childbirth, erosions, eversions and leukoplakia must be recognized and considered as precursors of malignancy.

Early diagnosis depends upon determining the cause of any deviation from the normal menstrual cycle and of any vaginal discharge. Pain, hemorrhage and an odorous discharge are symptoms of late carcinoma of the cervix. Biopsy is an invaluable aid in diagnosis, and should be used in any case where the slightest doubt of the true nature of the condition exists.

Radium therapy is the treatment of choice and is equally as effective in early carcinoma as in the late inoperable stages.

Symptoms referable to the rectum and bladder, urinary and fecal fistulae and benign stricture of the intestine are the usual complications of radiation treatment.

MANAGEMENT OF THE PATIENT WITH POLLEN ALLERGY

I. M. Hinnant, M.D., and Farris D. Evans, M.D.

It is the purpose of this discussion to present briefly the principles of management of the patient with pollen hay fever and asthma. Although pollen allergy may be manifested as a seasonal dermatitis or eczema, the majority of patients exhibit typical ocular and respiratory symptoms of hay fever or asthma or a combination of the two. Our presentation is limited to subjects with hay fever and asthma.

The problem of control of pollen allergy interests not only the allergist but many others engaged in the field of therapeutic medicine. It is at this time of year that patients with pollen allergy begin to contemplate the management of their problems. Fortunately, a small percentage of sufferers have been under the care of physicians and have received the perennial method of pollen hyposensitization which assures them some degree of relief from their symptoms in the future; however, the majority of patients are not under care and many will present themselves to the physician in the next few weeks or months.

It is estimated that between three and four million subjects in this country suffer with hay fever or asthma. Balyeat[1] states that approximately two per cent of the population suffer with this particular condition. Piness and Miller[2], after a survey of 4000 subjects in two communities on the West Coast, found that 4.4 per cent of the first group and 3.0 per cent of the second were hay fever victims. A similar survey in New York and vicinity was carried out by Cooke and Vander Veer[3] and revealed that 3.5 per cent of the total population suffered with hay fever or asthma. Such figures indicate that one out of every thirty subjects suffers with pollen allergy. This therefore makes management of the patient's problem of more than casual interest to the average physician.

Many phases of treatment are undertaken by both patient and physician. Unfortunately, economic circumstances permit only a few sufferers to visit the pollen-free areas. Pollen hyposensitization has been accorded most satisfactory results and promises today the best means of control of this particular problem. When Noon[4], in 1911, treated the first patients suffering from pollen hay fever and asthma by hyposensitization measures, only a small percentage of the patients obtained satisfactory clinical relief. Since that date, advances have been made both in diagnosis and therapy and this has resulted in an increasing high percentage of patients who secure satisfactory clinical relief. It is now conceded that from 90 to 95 per cent of the patients who undertake pollen hyposensitization treatment attain what they consider a satisfactory degree of relief from hay fever symptoms.

This is true of the patient suffering with simple hay fever symptoms. It is acknowledged by most workers that patients with pollen asthma are more easily treated than those suffering with simple hay fever.

The success of treatment of pollen allergy is dependent upon a number of principles. These remarks are based upon the data obtained in a study of 400 patients who came to the Cleveland Clinic in the past three years for diagnostic and therapeutic advice for the control of pollen allergy. Although a number of these patients were under our personal care, the majority were seen by us for diagnostic investigation, and therapy has been carried on by the home physician with suggestions as to management, the pollen antigens being supplied by us.

Patients who suffer with perennial allergic rhinitis, perennial asthma, or perennial bronchitis may be sensitive to pollens to a very mild degree, but other substances, either inhalants, such as house dust, feathers, animal epithelia, orris root, foods or bacterial infection, are the major factors in the production of the symptoms. In patients with pollen allergy, pollen sensitivity is by far the major factor. There is a distinct seasonal variation in the symptoms these patients experience, although many have exhibited mild symptoms throughout the other seasons of the year which were accounted for by various inhalant and food sensitivities. Our efforts, therefore, have been directed toward adequate knowledge of the plants which produce pollens that cause hay fever and the thorough control of these sensitivities.

The first requisite in the adequate control of the subject with pollen allergy is a botanical survey. The investigator must be acquainted with the pollen-producing plants that are indigenous to the section in which the patient lives and also the periods during which the plant blooms and discharges the pollen into the atmosphere. One recognizes that there are a great many plants in every locality. Many of these are capable of producing pollens that are exciting causes of hay fever. However, on close survey, the investigator finds that the majority of these plants are not present in sufficient abundance or do not discharge pollens in sufficient quantities to produce hay fever symptoms. The following requisites are necessary for pollens to produce hay fever and asthma.

1. The pollen must contain an excitant of hay fever.

2. The pollen must be wind-borne as regards its mode of pollination and must be carried a considerable distance.

3. The pollen must be produced in sufficiently large quantities.

4. The plant producing pollen must be widely and abundantly distributed.

After a careful survey of these requisites, one acknowledges that only a few plants fulfill all five requirements. We know that in Cleveland and vicinity a definite number of trees, a few grasses, and two weeds are the principal producers of pollen which cause symptoms of hay fever. In recent years, local botanical surveys have been carried out by men interested in the control of pollen allergy and fairly accurate data have been accumulated regarding the distribution, the abundance and the time of pollination of the plants producing symptoms of hay fever. For those interested in the control of pollen allergy, knowledge of the local situation regarding pollen hay fever producing plants can be obtained through: (1) a careful study of the surveys, (2) through field trips and (3) through daily pollen counts. We found it necessary in our work to make frequent visits into the surrounding country during the hay fever season in order to ascertain just how abundant the plants were, what types were present, and when the plants were pollinating. For three years, we have carried out daily pollen counts according to the method of Mr. O. C. Durham, chief botanist of the Abbott Laboratories, Chicago.

Our pollen counts over a period of three years have included counts in the grass and weed pollen season. The work this year includes a daily count during the tree pollinating season in an effort to secure a most thorough knowledge of the trees which produce pollen hay fever in this vicinity. The greatest value of daily pollen counts is knowledge concerning the plants producing pollen in the surrounding section, as well as the type, abundance and time of appearance and disappearance of pollen in the atmosphere. Likewise, they have been valuable in attempting to interpret hay fever symptoms during the active season. As noted, their greatest value is as a diagnostic aid. However, during the hay fever season the pollen counts are distinctly advantageous to patients undergoing coseasonal treatment because it aids in regulating the correct dosage of pollen antigen for the patient. Therefore, the first requisite in diagnosis of pollen allergy is a careful and thorough botanical survey of the abundance of plants and their type, and a pollen calendar in which daily pollen counts are recorded.

In Ohio and the surrounding section, there are three distinct hay fever seasons; the tree, the grass and the weed. The tree season begins about the last week in April and reaches its height the last two weeks of May, continuing through June. The pollen of the silver maple is usually the first to be detected in the atmosphere. This is closely followed by elm pollen and later the pollens of poplars and willows. The pollen of the oak tree, which is the most abundant and the principal cause of tree pollen hay fever appears during May and is present well into June. This produces a definite overlapping effect with the grass hay fever

season. Trees other than elm, poplar, willow and oak which produce pollen in Ohio and the surrounding sections are ash, black walnut, hickory, sycamore, birch, beech and box elm.

The grass hay fever season begins about the third week in May, reaches its height the third week in June and tapers off gradually to a nonactive stage about the second week in July. The season of 1935 was definitely prolonged due to climatic conditions, the pollen being present in the atmosphere in a sufficient quantity to produce hay fever until the first week in August. A careful review of patients suffering with grass hay fever confirms these findings as suggested by the daily pollen count. The grasses producing hay fever in Ohio and surrounding sections are orchard grass, June grass, Redtop and Timothy, and it is generally acknowledged that the Timothy pollen is most abundant and produces the most trouble. Most workers use a large percentage of Timothy pollen in treatment of patients with grass hay fever. Plantain begins to pollinate in May and continues throughout the greater part of the summer but, in so far as our studies are concerned, the pollen is not present in sufficient quantity to be an actual excitant of hay fever. Other than the grasses mentioned, we do not believe there are any of clinical significance in this section of the country.

The fall hay fever season begins approximately August tenth to fifteenth, according to local weather conditions. Giant and short ragweed pollens produce at least 95 per cent of the pollen appearing in the atmosphere during August, September and October. In Ohio and the surrounding sector, we see pollen-producing weeds which are active excitants of hay fever, but the scarcity of such weeds prevents them from being a factor in the production of clinical hay fever.

In making daily pollen counts over a period of three years we have not been able to recognize or identify any type of weed pollen other than ragweed. Clinical study likewise emphasizs the fact that immunization to ragweed antigen produces excellent clinical relief if other existing allergy is controlled. We routinely include in our studies pollen tests with all weed and grass families. Reactions to these pollen antigens are commonly elicited but no clinical significance can be established in regard to patients' hay fever problems.

One immediately raises the question of the proper approach to the problem of the patients with pollinosis. One dictum deserves emphasis. These patients with allergy must be individualized both as regards to investigation and to treatment. The first and most important step in this plan of individualizing the patient is to elicit a detailed history. The character of the symptoms and the onset must be determined with accuracy because these are to be correlated with our knowledge of the pollen

seasons. The effect of various climatic conditions on the general health is a point of especial value, particularly in this area where the seasonal variations and weather are definitely unfavorable to patients with allergy. Seasonal hay fever during the late winter and early spring is often complicated by acute infection in the nose and, therefore, the differential diagnosis between chronic infection, rhinitis and allergy is not easy. The personal history should always include information regarding the number and frequency of colds, various data relating to other acute upper respiratory infections, and a careful history of nasal surgery. In our investigation of patients with allergy, particularly pollen allergy, approximately 30 per cent of these patients exhibit evidences of hypometabolism or else true hypothyroidism. Certainly, one should not overlook a glandular disorder such as this in attempting to obtain the best clinical results. Chronic focal or systemic infection should never be overlooked. Dietary habits, modes of living and any environmental factors should be investigated. Although only of academic interest, it is of definite advantage to make a careful inquiry regarding any family history of allergy.

In addition, every patient should have a thorough physical examination and a careful examination of the nose and throat. As a rule, only the typical findings of allergy will be revealed on examination of the nasal passages. At times, mechanical barriers, such as a deflected septum, spurs and even occasionally chronic sinus infection and nasal polypi will be found which definitely would prevent a satisfactory recovery unless removed. It is our belief that these mechanical barriers should be corrected before the advent of the pollen hay fever season. Certainly, no work should be instituted during the active hay fever season. From the correlation of the history and the physical findings, special examinations may necessarily be indicated to disclose or exclude pathological conditions which would affect the general health of the patient. Routine blood counts, blood Wassermann test and blood sugar estimation are always carried out. We do not make nasal smears for eosinophilia because it is our impression that blood eosinophilia is fairly constant in a high percentage of these patients. Chronic infectious processes of the upper respiratory tract are present in many instances during the early hay fever season, and the value of the red blood cell sedimentation rate is certainly worth considering in differentiating between infection and simple allergic reaction.

Following the preliminary examination, complete and thorough tests for allergens are made. In patients with seasonal hay fever, the investigation should never be limited to pollens alone. It is the experience of investigators in the field of allergy that one of the greatest causes for

failure to obtain a satisfactory clinical result is inadequate investigation as well as inadequate treatment. Workers in allergy recognize the importance of standardized, reliable potent extracts for skin testing, and they agree that such study is dependent upon minutely detailed searching, and that considerable time and effort are necessary to procure satisfactory results. Failure usually results when the investigation is carried out with a limited number of allergens that were purchased as a special offer from some commercial supply house. Emphasis should be placed upon the necessity of reliable potent extracts for pollen investigations as well as testing for inhalant and food allergens.

Several methods of testing for various allergens are available: these include the scratch, intracutaneous and the passive transfer method. The patch tests with the oil or the whole pollens are of value when pollen allergy is a suspected factor in cutaneous lesions. The choice of the method of testing is made as soon as it is decided that any seasonal variation in symptoms is present. Patients with a definite history of seasonal variation in their symptoms should always be tested with pollens by the scratch method, using the flexor surfaces of the arms. This procedure will prevent systemic reactions, which are discouraging to the patient as well as the physician. For epidermals, inhalants and foods, the back of the patient presents the best site for testing for several reasons: It provides an ample area for a large number of tests, a skin of fine and consistent texture, a blood supply which is constant, and an area that renders interpretation of the skin reactions more uniform and accurate. When tests are made on the arms, from five to six visits are required, whereas the use of the back permits from one hundred and fifty to two hundred tests to be completed in two and not more than three sittings. The number of tests that can safely be made on each visit depends upon the state of hypersensitivity of the patient, the strength and potency of the extracts, and the reaction of each individual to the substances. The tests should include all the possible offending allergens. In our experience one hundred and fifty to two hundred includes every angle in the average case of pollen allergy. Occasionally a repetition of the tests is necessary but, as a general rule, visits on two days will suffice for a complete examination and investigation for allergy.

Ophthalmic and intranasal tests for suspected allergenic substances have their place in the allergic survey. These tests are performed by simply placing in the conjunctiva or blowing against the nasal mucosa small quantities of purified dried powder of the substance that is suspected. If hypersensitivity exists, an immediate reaction is noted, and the substance can readily be washed out with normal saline and weak adrenalin solutions. Often a severe reaction occurs, which may be

discomforting to the patient for a few days. Because of this undesirable reaction, and because testing by scratch, intracutaneous and passive transfer methods are reliable in pollen allergy, we have not employed ophthalmic and intranasal tests. In complete investigations of more than 3000 patients over a three year period, we have noted only three patients with pollen allergy who failed to respond by direct methods of skin testing. It is obvious that refractive skins are practically unknown in pollen allergy.

The fallibility of determining allergens by skin testing has received considerable criticism from time to time. In most instances, criticism has been stimulated by the failure to identify the causative agents and the number of false positive reactions that are occasionally encountered. Undoubtedly, skin tests are not accurate in 100 per cent of the cases, but it is true that skin testing, in the hands of an experienced worker who uses reliable and potent extracts, gives a working knowledge of the patient's problem which cannot be paralleled by any other known diagnostic procedure. In pollen allergy, skin testing gives the highest degree of accuracy. These tests give reliably accurate results in 90 per cents of the patients.

Certain precautions must be taken in testing hay fever patients. A solution of epinephrine (1:1000) should always be available during testing. During the procedure of testing, the patient should be questioned as to any known idiosyncrasy before each test substance is used.

Therapeutic Methods

In pollen allergy, sensitivity to pollen is the largest factor. Only a few patients have the opportunity of visiting pollen-free areas. Hyposensitization to the specific offending pollen therefore is imperative. Is it acknowledged among workers in allergy that pollen hyposensitization by the accepted methods will give 90 per cent of sufferers adequate relief of symptoms? What methods are to be adopted to carry out therapy which results in such excellent clinical relief? It has been noted previously that each patient must be individualized, both as to investigation and to therapy. Complete survey of the patient's problem is necessary; this includes not only tests for pollens of suspected trees, grasses, weeds, but also a careful interpretation of the allergens other than pollen, and strict adherence to the prescribed routine of elimination or hyposensitization. Occasionally, we have seen a patient with seasonal hay fever and asthma who could not be hyposensitized, but who had very little discomfort during the pollen season because he had strictly eliminated all epidermal, inhalant and food substances to which he was found sensitive. This is not the method of therapy to be advised, but it does illustrate that allergens other than pollens play a part in the pro-

duction of patients' symptoms. For this reason, we stress the advisability of a strict allergic regimen, particularly before and during the active hay fever season.

Three methods of therapy may be used in hyposensitization procedures—coseasonal, preseasonal and perennial.

Coseasonal Hyposensitization: The patient who is seen at the onset or in the middle of the hay fever season and who has had no form of therapy presents a difficult problem. For many years, it was considered undesirable to begin treatment during the active hay fever season but, in recent years, many workers have adopted a plan of coseasonal treatment which is devoid of any danger to the patient and results in satisfactory relief of symptoms in from 60 to 70 per cent of the cases. The first procedure with the untreated patient suffering acutely with hay fever and asthma is to completely investigate the allergy, prescribe a strict routine, limit activities, prescribe mild symptomatic measures and institute very small doses of pollen antigen at frequent intervals. The doses of pollen antigen under these circumstances deserve more than a casual note. The initial dosage should be from 5 to 30 pollen units, (0.05—0.3 cc. 1:10,000 solution) with repeated injections at one or two day intervals, gradually increasing the dosage to not more than 80 or 100 pollen units. As the season advances, an optimum dosage of 150 or 200 units may be used, but in our practice, we never use more than this amount. Such minute doses of antigen given two or three times a week will result in excellent relief of symptoms. More care should be exerted and smaller dosage should be administered if one is dealing with hay fever and bronchial asthma. The asthmatic tends to get an overdosage very easily, with consequent intensification of symptoms.

Preseasonal Hyposensitization: Most physicians use the preseasonal method of hyposensitization. The patient reports to the physician two, three, four or five months before the expected hay fever season begins. Allergy tests are made and treatment is carried out with pollen extract based upon the patient's history, results of skin tests and knowledge of the patient's environment. Treatment is instituted with small doses of pollen antigen, 10 to 30 units, and the dosage is increased at each injection unless an undesirable reaction is obtained until an optimum dosage is reached for the individual patient. This is usually between 3000 and 6000 units of pollen antigen. With the onset of the hay fever season, the dosage is decreased to approximately 2000 or 3000 pollen units, and maintained at this level until the active pollen season ends. The inoculations are given at intervals of twice a week until a substantial dosage is obtained and then continued at weekly intervals until the close of the hay fever season.

Perennial Hyposensitization: Today, many workers are advocating the perennial method of hyposensitization in the treatment of pollen allergy. A close analysis of opinion concerning this method discloses no points of disfavor and many advantages. Briefly, the advantages may be stated as follows:

1. Intensive preseasonal or coseasonal treatment is avoided.

2. The tendency toward unfavorable local or systemic reactions is decreased.

3. Contact between patient and physician is established and maintained throughout the year. The value of this feature can hardly be overestimated. Many deviations of a patient's health from normal may be corrected in the early stages if he is under the close observation of a physician. We have also found it opportune in a number of patients taking the perennial method of therapy to institute other measures of hyposensitization, particularly to house dust in the domestic and to bacterial vaccines in the patients who exhibit a definite tendency to upper respiratory tract infections during the fall, winter and spring seasons.

4. Treatment may be instituted at any time of year; this enables the physician to distribute his work more evenly throughout the year and to avoid a preseasonal or coseasonal rush of hay fever sufferers.

5. Perennial hyposensitization permits the patient privileges of vacation and travel. Most patients seek vacation during the summer or early fall months when pollen is heaviest in the atmosphere. The perennial method of therapy presents a convenient aid to the patient in this respect.

6. The final point of advantage and probably the one of greatest significance in control of pollen allergy is that the perennial method of hyposensitization offers some promise of a permanent immunity. One does not work with hay fever and asthma patients for any length of time before he realizes that this is the point of interest to the patient. That permanent immunization can be effected in a large percentage of patients if thorough and consistent therapy is carried out is beyond any pale of doubt. Walker[5] reports cures in 26 per cent of his patients after preseasonal treatment extending over a period of years. If excellent results are obtained with preseasonal hyposensitization over a period of years, perennial treatment should yield equally good or superior results. Observation of a large group of patients receiving the perennial method of therapy over a period of years will answer this question.

A certain percentage of patients with pollen allergy report for investigation during the fall and winter seasons for hay fever, asthma or some other allied allergic state and begin the perennial method of therapy.

However, the majority of patients enter the all year method of treatment after an intensive preseasonal or coseasonal course of therapy has been followed. Instead of discontinuing dosage, the patient continues to take pollen antigen injections at weekly intervals, the dosage being gradually increased to a maximum level which may be any amount between 3000 and 30,000 pollen units, depending upon the individual case. It is agreed that the results in an individual problem do not depend upon giving a large amount of pollen antigen, but rather upon the reaction of the patient to immunization procedures, regardless of the amount of antigen employed. Injections are best continued at weekly intervals through the first year of therapy. Less frequent intervals may be employed in the late years of pollen therapy, but the interval should never be greater than two weeks. In this respect, we differ with the commercial supply houses, who are extensively advertising their pollen extracts for the perennial method of hyposensitization and advising that injections be given once a month. Satisfactory immunity cannot be obtained with such infrequent injections.

Certain points should be emphasized in regard to the technic of pollen therapy. Too severe local reaction or any sign or symptom of systemic reaction should be avoided. Signs and symptoms of constitutional reaction indicate shocking of the tissues and not stimulating immunity. It is far more advantageous to give a subreaction amount of pollen antigen throughout the course of therapy than to encounter one general reaction. If such a reaction occurs, the dosage should be decreased to a safe level, several injections of this amount being given, and then the dosage should gradually be increased again.

The possibility of giving the pollen extract intravenously should be avoided. By careful aspiration of the syringe after the needle is placed in the subcutaneous tissues, this possibility, as a rule, can be eliminated entirely, but occasionally an error in overdosage is made. Immediately, a tourniquet is placed above the site of injection, a 1:1000 solution of adrenalin is injected in and about the site where pollen antigen was given and small amounts of epinephrine are injected into the opposite arm. After a few minutes, the tourniquet is slightly loosened for a few seconds and then reapplied. The tourniquet is alternately tightened and loosened for a period of thirty minutes, permitting small broken doses of antigen to reach the vital tissues. The patient should be kept under observation for a period of two or three hours and, if discharged, very complete instructions should be given to the patient or relative for the use of adrenalin in case a delayed reaction occurs in six, twelve or twenty-four hours. Many serious reactions can be avoided by the use of this simple technic.

MANAGEMENT OF THE PATIENT WITH POLLEN ALLERGY

Patients who have received injections of pollen antigen should be kept in the office for 20 or 30 minutes in order to observe and control any constitutional reaction. If reactions are to be noted, they will usually occur in this period of time.

The question of securing potent and reliable pollen extracts for testing and treatment purposes arises. Many commercial supply houses offer perfectly satisfactory antigens in standardized dilutions for therapy in the average case. The antigens are usually prepared in groups, such as the "Spring type," the "Fall type" or a mixture of the two. One immediately recognizes the limitations of this type of therapy and the lack of individualization for each allergic patient; furthermore, no complete allergic survey has been made, and no correlation is possible between the clinical history and suspected allergens. It is conceivable that any method of therapy directed along these lines would result in satisfactory relief in the average patient, but would fail in the patients whose conditions deviated from the normal.

Many physicians have availed themselves of diagnostic allergy units whereby complete investigation may be carried out. Treatment sets of pollen antigen may be prepared according to correlation of clinical history, skin reactions to pollens, and a thorough knowledge of the pollen flora in the patient's environs. In this way, not only are more accurate methods used in planning therapy, but the patient is given the opportunity of availing himself of knowledge concerning his own allergic state and regarding allergic factors discovered in testing, and he is also stimulated to study his allergic problem. Practically all workers in allergy prepare their pollen extracts and supply treatment sets to the family physician; these are accompanied by detailed instructions regarding the administration and suggested schedule of dosage. Such a plan of coöperation between the allergist and family physician assures the patient of keener interest in his problem and ultimately of more successful relief of symptoms. In the past three years, we have followed this plan of coöperation with the family physician in more than 300 patients. Results in this group of patients have been very gratifying, and a high percentage have secured satisfactory relief of symptoms. It is needless to state that the average hay fever sufferer is dependent upon his family physician for ultimate control of his problem and we believe the results obtained by the concurrent and coöperative efforts of a central diagnostic allergy unit with the patient's private physician will lead to a better knowledge and control of the pollen allergy problem.

Regardless of every effort, a certain percentage of patients will be found who have discomforting hay fever and asthma symptoms during the most severe days of the pollen season. A discussion is incomplete

without some mention of measures to afford relief of the acute symptoms.

If the patient has rather acute symptoms, the following measures should be considered:

Limit activities.

Avoid undue exercise, heat and fatigue.

Stay out of the country, off golf courses, avoid swimming by all means and do not drive more than necessary.

Eat lightly. Carefully check the diet for known or suspected food allergens. If any uncertainty exists, eliminate common food allergens such as wheat, eggs, milk, potatoes, tomatoes, etc.

Insist on normal gastro-intestinal elimination.

Avoid flowering plants. Check house for any possible flowers and remove these and have the room thoroughly cleaned.

Avoid contact with house dust and smoke-congested rooms.

Remove from environment any known or suspected epidermal or inhalant allergen.

Beware of cosmetics. Use the non-allergic brands of cosmetics that can be obtained at any good pharmacy.

In effect, keep in mind that any substance may be aggravating the patient's symptoms.

Drug therapy is necessarily limited, and when employed should be mild.

Eye drops of the following composition are helpful:

℞ Holocain hydrochloride ..... gr. 2
Zinc sulphate ..... gr. ¼
Adrenalin 1:1000 ..... ʒ 1
Distilled water qs. ad. ..... ʒ 1

Sig. 2 - 3 drops in each eye, 3 - 4 times a day.

Eye washes of boric acid solution or normal saline serve to relieve the average sufferer. If edema of the conjunctiva is marked, ten drops of a 1:1000 solution of adrenalin added to an eye cup of normal saline solution gives good relief. Shaded glasses are quite helpful. Ice water compresses applied to eyes several times daily will allay irritation and give a sense of comfort.

The nasal passages are best untreated unless symptoms are severe. In this case, a nasal spray of 1 per cent aqueous solution of ephedrine sulphate with five grains of metycaine to one ounce is helpful. If the patient is irritated by ephedrine, it is best to resort to a weak solution

of cocaine, such as 2 per cent cocaine hydrochloride which is used as a nasal spray. Under no circumstances is local nasal medication to be used unless the patient's discomfort demands such therapy. Oily solutions such as nose drops are as a rule irritating. It is always advisable to use an atomizer in order to secure a more uniform distribution of the medicament to all surfaces.

For oral administration, preparations of ephedrine, atropine and aspirin are commonly used. Before prescribing drugs, the patient should be questioned carefully as to knowledge of any drug sensitivity. It is easily recognized that oral administration of any drug in doses that will not produce toxic effects can be of only limited value to the patient who has severe hay fever or asthma. In our experience, drug therapy by the oral method is of little value, although one may find the exceptional patient who responds nicely to small amounts of the drugs mentioned above.

When the patient with pollen asthma is acutely ill, bed rest is imperative. All of the preceding precautions should be exerted fully, particularly the necessity for a liquid or light diet, plenty of hot drinks, good gastro-intestinal elimination, care of any possible inhalant or food allergens. Ephedrine or ephedrine and amytal may control the paroxysms. The use of a 1:1000 solution of adrenalin hypodermically, as necessary, or the use of the newly marketed adrenalin 1:100, inhaling the fine mist from the nebulizer, is indicated in the more severely ill patients. There is no advantage in withholding adrenalin, permitting the patient to suffer one paroxysm after another because this tends only to exhaust and weaken him. A small dose given in the early stages of an attack will prevent many severe paroxysms. In our experience, morphia is usually disastrous, atropine is contraindicated in almost 100 per cent of the cases, and iodides are of questionable value in the acute stage. The same is true of preparations of calcium. Mild sedation is indicated in the average patient since it removes some of the restlessness and anxiety. *The best form of therapy is the institution of investigation and control of the patient's allergic problem to prevent such a recurrence in the future.*

Summary

Adequate control of pollen sensitivity is the largest factor in pollen allergy. Hyposensitization measures have resulted in excellent clinical relief in the majority of patients with pollen allergy. Failure to obtain satisfactory relief is due to inadequate investigation and inadequate treatment. We have summarized our methods both from diagnostic and therapeutic angles of caring for pollen allergy sufferers. Our results are based on the studies of 400 hay fever asthma patients seen at the Cleveland Clinic in the past three years. Emphasis is placed on adequate investi-

gation and individualization of treatment in every case. Our results lead us to believe that the problem of pollen allergy can well be cared for if the principles of diagnosis and treatment noted in this presentation are effectively carried out.

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THE VALUE OF THE UREA CLEARANCE TEST

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Renal function has to do with the maintenance of the normal constitution of the body fluid—in other words, with the preservation of an optimum internal environment for the body cells. The kidney, in excreting an excess of water with the end-products of nitrogenous metabolism, must exercise a certain degree of discrimination in regard to the excretion of inorganic salts and other so-called threshold substances, depending upon the body need. The importance of such a basic function renders necessary the development of accurate methods for the estimation of renal efficiency. It is not to be expected that any one simple test can be used as an accurate index of the efficiency of an organ whose task involves multiple processes and whose function is influenced from without through nervous connections and hormone control.

Certain phases of renal activity have been used as a basis for tests which may grossly be classified as excretion and retention tests. Excretion tests may be subdivided into (1) those which utilize the estimation of substances normally excreted, and (2) those in which a foreign substance is employed in making the test. The former includes the water test, concentration and dilution test, Mosenthal test, the creatinine test of Major, the urea concentration test of MacLean and the urea clearance test of Van Slyke. The tests in which a foreign substance is employed include the phenolsulphonphthalein test of Geraghty and Rowntree, the indigo-carmine and all dye tests.

In retention tests, an estimation is made of the level in the blood of the nitrogenous metabolites, urea, creatinine and uric acid. Inasmuch as these are maintained at a constant level until renal reserve is lowered to approximately one-fifth of normal, these retention tests are significant only (1) in the terminal stages of a renal lesion, (2) in the acute stage when renal function is temporarily in abeyance as a result of swelling and inflammation, or (3) in obstructive lesions, especially those associated with prostatic hypertrophy where renal function is at a low level in consequence of back pressure.

For the urea clearance test, simultaneous readings of the blood and urinary urea and the urinary output per minute are required. The urine is collected at two successive hourly intervals, the bladder being completely emptied before the beginning of the first period, and midway between the two periods, a specimen of blood is taken. In this way, two tests of the kidney function are made, the one blood urea estimation serving for both, since this varies little over a considerable period of time. The exact period of the collection of urine need not necessarily be limited to an

hour, provided an accurate record is kept of the time so that the minute volume of urine can be calculated from this. The urea content of the urine and the blood is then estimated and applied in the following manner: If the urinary flow exceeds 2 cc. per minute, the clearance is calculated according to the formula: Maximum clearance $= V \times \frac{U}{B}$. V is the urinary volume per minute, U the urinary urea per cc. and B the blood urea per cc. If the urinary flow is less than 2 cc. per minute, the clearance is calculated according to the formula: Minimum clearance $= \sqrt{V} \times \frac{U}{B}$ An average normal for the maximum clearance is 75 cc. and for the minimum clearance, 54 cc. Results are usually expressed in percentages of normal, and this may be obtained by multiplying by the factor 1.33 in case of maximum clearances and by 1.85 in case of minimum clearances. For description of the technic of tests and calculations, the original articles by McIntosh,[1, 2, 3] Möller[2, 3] and Van Slyke[1, 2, 3, 4] may be consulted. Recently, minor changes have been made in the technic in that it has been shown that the time of day is of little significance and that, in the majority of cases, the patient may be up and around during the test. The use of moderate amounts of coffee has also been shown to be of little consequence.

The urea clearance test possesses the advantage of utilizing a material normally excreted and one which constitutes approximately one-half of the urinary solids, since the average adult urea excretion for 24 hours is 60 grams out of a total solid of 125 grams. Furthermore, according to the modern theory of renal function, the excretion of urea is a function of the glomeruli; thus, the urea clearance test is a measure of the function of that most essential portion of the renal unit, the glomeruli. It is not assumed that the urea clearance formulas express with mathematical accuracy the complete effect of all factors governing urea excretion; rather, they are only expressions of the effect of two factors—blood urea content and urinary volume—which are in continual action and appear to be ordinarily of most importance in regulating the urea output.

In normal individuals, urea clearance tests at different times may indicate a wide variation in results. Thus in normal persons, Van Slyke found variations of from 35 to 75 cc. per minute in standard clearances and in maximum clearances, variations of from 50 to 100 cc. per minute. Furthermore, in the same individual, tests at different times gave as much as 25 per cent variation in results without any evidence of change in renal function. It is evident that other factors, in addition to blood urea concentration and urinary volume, affect urea excretion. Addis and Drury[5] found that the maximum clearance was increased by ingestion of a mixed meal—milk, caffine and glutamic acid—and de-

creased by pituitrin and very large doses of adrenalin. On the other hand, small doses of adrenalin increased excretion. These factors may exert their influence by varying the blood flow through the kidneys or they may alter directly the excretory ability of the kidney.

The results of the urea clearance tests which had been done at the Cleveland Clinic in a period of two years were reviewed in an attempt to evaluate the accuracy of the test as compared with other renal functional tests and with the clinical diagnoses. The patients on whom these tests were made included a large number without demonstrable renal lesions, as evidenced either by physical examination or urinalysis. Almost without exception, the patients in whom there was no evidence of renal disease showed clearance values ranging from 75 to 100 per cent of normal. Severe hyperthyroidism appeared to increase the clearance value slightly, perhaps in accordance with the increased flow of blood. Acute infection decreased the results slightly while malignant growths appeared to have no definite effect unless the urinary system was involved. In one such case in which a carcinoma of the pelvis was present involving the ureters, clearance values of 13 and 12 per cent were obtained. From the age of 50 onward, clearance values appeared to be reduced. Peripheral arteriosclerosis also was frequently associated with low clearance values; this suggests that pathological changes in the renal arteries may so reduce the flow of blood that urea excretion is considerably hampered. The study of approximately one hundred patients who had no evidence of renal lesion but who did have a variety of other lesions makes it seem probable that urea clearance values are not affected to any significant degree by conditions external to the kidney or urinary tract.

It is evident that, in common with other organs, there is a renal reserve factor which may be depleted over a long period of time before a point is reached where clinical evidence of such reduction occurs. It is likewise possible that a portion of the renal function may be lost before any appreciable diminution of the urea clearance value is obtained. In one instance, an apparently normal kidney had to be removed as a result of an accident, and five days after nephrectomy, urea clearance tests showed 62 per cent function. In other patients, higher values have been obtained from the kidney remaining after nephrectomy, but these were mostly patients in whom a functionless kidney had existed for some time, and in whom hypertrophy of the remaining kidney might well have occurred.

Three hundred cases of renal disease have been selected for study. Detailed investigation has been carried out and some of the patients have been seen on repeated occasions. These cases have been grouped

according to the classification of Addis.[6] Exact classification is a matter of opinion in some instances, especially since postmortem examinations have been possible in only a few.

Fifty-four of these cases fall into the group of hemorrhagic Bright's disease in varying stages. It has not been our privilege to observe any severe cases of the initial type. In three rather mild and subsiding cases, clearance values ranged from 40 to 60 per cent of normal without any evidence of nitrogen retention. Opportunities to recheck these patients at later times have been rather rare, but in two cases, definite increase in function was found some months after the initial test although in neither case had there been a return to the normal standard. Van Slyke[7] has reported cases of acute hemorrhagic Bright's disease with uremia in which the urea clearances were below the critical 20 per cent level. These levels markedly increased following the patients' recovery, and Van Slyke feels that the results vary with the healing process.

Sixteen of our patients were in the chronic active stage of the disease and the clearance values were definitely reduced, ranging from 60 to 20 per cent. Hypertension and urinary evidences of chronic hemorrhagic Bright's disease were manifested in these patients. Several were rechecked after a period of months and little change was noted, although the general tendency was downward. Unfortunately, most of our patients with the hemorrhagic type of Bright's disease were in the terminal stage on admission to the hospital and the urea clearance values were in the level below the critical 20 per cent. Uniformly, these patients had clinical evidence of uremia with characteristic blood chemistry findings.

Eighteen cases of degenerative Bright's disease are included in this series. Even with massive edema and heavy proteinurea, these patients had urea clearance values which frequently were close to normal. Inasmuch as postmortem examination in such cases shows tubular degeneration as the outstanding pathological feature with relatively good glomeruli, the clearance value theoretically should be good. At the first observation, the levels ranged from 40 to 80 per cent of normal. In one case, a blood urea of 66 milligrams per cent accompanied a 40 per cent clearance level. In two patients who have been followed for some months, however, marked decrease in the clearance values has accompanied clinical evidence of a downward progress. One patient had a clearance of 95 per cent when he was first seen and this decreased to 76 per cent in six months. In another case, the level progressively decreased from 60 per cent to 16 per cent in a period of nine months and the patient died with definite manifestations of uremia. Postmortem examination confirmed the diagnosis. From our study of these interest-

ing cases, it would seem that the course, in adults at least, is progressively downward and usually terminates in renal failure if the common intercurrent infections are escaped.

In 228 patients in this series—76 per cent of the entire group—the lesion evidently was of vascular origin. Such a diagnosis is made chiefly from a family history of vascular disease, absence of antecedent renal history or infection which usually is associated with renal disease, such as scarlet fever, the history of insidious onset or the accidental discovery of hypertension coupled with evidence of vascular disease in the eyegrounds and the absence of the findings in early stages of urinary disease. It is possible that a certain number of these were advanced cases of the hemorrhagic type in which the onset had been insidious, and in which the clinical findings could not be definitely separated from those of primary vascular disease.

Senile arteriosclerosis involving larger arteries appears to reduce renal function only by degrees as the circulation through the kidney is impaired. Such patients have a mild reduction in clearance values, but it is evident that they do not have a progressive renal lesion and that there is little disturbance of glomerular activity.

Younger individuals who have hypertension without urinary signs frequently exhibit normal clearance values. However, when albumin and occasional casts are present in the urine, some reduction may have occurred, although some patients seem to carry on over long periods without any demonstrable kidney defects. Reduced urea clearance is particularly true in those patients who have a persistent elevation of the diastolic pressure, although this is not absolutely constant. With the onset of well-marked vascular changes in the fundus and increased signs of urinary disturbance, urea clearance values become lower in harmony with the deterioration of health generally. Several such cases have been seen when the terminal stage had been reached in which the clearance values were around 10 per cent and marked nitrogen retention was present. The rate at which the process progresses appears to vary considerably. One patient of 40 years has a marked family history of vascular disease and his blood pressure has been at least 200 mm. systolic, 120 mm. diastolic for the ten years we have observed him and still his clearance is 65 per cent. However, in several others, there appears to be a very rapid process with marked hypertension, marked vascular changes in the eye, urinary findings suggestive of the hemorrhagic type of Bright's disease, and rapid reduction of clearance values suggesting the development of a progressively rapid renal deterioration which corresponds to the malignant hypertension of Volhard and Fahr.[8] Thus in one patient whose blood pressure was 260 mm.

systolic, 140 mm. diastolic, the urea clearance value was reduced from 55 to 14 per cent in six months. Clinically, this patient had a rapidly progressive downhill course, ending in uremia and the urea clearance test corresponded with this very closely.

In reviewing these cases, it has been possible to form some ideas regarding the comparative value of the urea clearance test and the phenolsulphonphthalein test. When all patients with renal disease are considered, it appears that the phenolsulphonphthalein test gives higher values in the more efficient kidney and shows little reduction in results until the urea clearance values reach an average of 60 per cent; then the phenolsulphonphthalein values fall more abruptly and tend to become equal to clearance values at about 30 per cent. From this stage, the phenolsulphonphthalein values are consistently below the clearance results, and below clearance values of 10 per cent, the phenolsulphonphthalein test shows practically no excretion. According to Van Slyke, the phenolsulphonphthalein test improves before the urea clearance when the patient is recovering from acute hemorrhagic Bright's disease. This may be a useful finding in the prognosis in some cases. In our experience, the phenolsulphonphthalein test values in the degenerative type tend to be higher than the clearance values by a greater margin than in other forms of renal disease. It would appear that, although the two tests tend to approximate each other, the urea clearance test seems to reflect the actual state of the kidney more accurately. The urea clearance test also is not affected by bladder retention which will alter the results of the dye test unless a catheter is used.

Summary

1. The simultaneous comparison of urinary and blood urea levels offers a method of checking the glomerular function.

2. The results obtained should not be considered as mathematically exact, but rather as an expression of the two main factors in the urea excretion, namely, the blood urea content and the urinary volume.

3. Considerable variation in the results of the urea clearance test in normal individuals and in the same individual at different times has been noticed.

4. Reduction in renal function is evidenced by lessened urea clearance values. Values below 20 per cent are apt to be accompanied by evidences of renal failure and if they are below 10 per cent, death usually occurs in a short time unless these levels are due to transient renal conditions which may be corrected.

5. For medical purposes at least, the urea clearance test would appear to be more accurate than the phenolsulphonphthalein test, and it constitutes the best single test of renal function which has been devised.

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THE DIAGNOSIS OF BRAIN TUMORS

W. James Gardner, M.D.

The purpose of this paper is to describe briefly the history and physical findings in a few of the more common types of intracranial tumors, namely the gliomas, the meningiomas, the pituitary and the acoustic tumors.

Strictly speaking, the glioma is the only true *brain* tumor, that is, it is the only tumor arising from the brain tissue proper. The meningioma arises from the membranes covering the brain, the pituitary tumor arises from epithelial cells of the anterior lobe of the hypophysis and the acoustic tumor arises from the sheath of the eighth cranial nerve. The glioma, or true brain tumor, however, does not arise from the functioning nervous elements of the brain but from the supporting or glial tissue from which it derives its name. The glioma therefore may be compared to the sarcoma arising from connective tissue. There are four commonly encountered types of gliomas classified according to cell morphology and some twelve more or less common types.

The neurological surgeon is no longer content to diagnose and correctly localize an intracranial tumor, but, with increasing knowledge of the life history of the various types of tumors, he attempts to predict the exact histological structure in each case as it confronts him. It is not merely to satisfy his vanity that the surgeon thus attempts to foretell the histological structure of the tumor with which he is about to deal. This foreknowledge permits him to plan his operative approach more satisfactorily and to deal with the neoplasm more adequately than he otherwise could.

Increased Intracranial Pressure

The symptoms commonly encountered in all types of intracranial tumors are the symptoms of increased intracranial pressure. These symptoms are headache, vomiting which is frequently projectile and unassociated with nausea, failing vision due to choking of the optic discs and in the late stages, a blunting of the intellect. There are, of course, conditions other than tumor which may increase the intracranial pressure and produce this same train of symptoms, the most common being meningitis, brain abscess and traumatic hematoma. However, if these symptoms appear gradually and without a history of a preceding infection or head injury, these other conditions can be eliminated.

There are only two reliable methods of determining the presence of increased intracranial pressure. They are ophthalmoscopic examination and spinal puncture. Edema of the optic discs due to increased intracranial pressure is readily recognized by fundus examination. If this is present, it renders spinal puncture unnecessary. The presence of increased intracranial pressure cannot be determined by spinal

puncture without employing a spinal manometer. The estimation of pressure by observing the rate of flow of the fluid from the needle is absolutely unreliable in most instances.

Increased intracranial pressure with its attendant symptoms, however, is not invariably present in patients with brain tumor. As might be expected, it appears earlier and progresses more rapidly in the more malignant types of gliomas while it comes on later and progresses more slowly in the meningiomas. In pituitary tumors, it is very seldom encountered for the simple reason that, because of the location of these growths, they are apt to cause complete blindness by direct pressure on the optic nerves before they can attain sufficient size to increase the intracranial pressure.

Brain Tumor in Children

Usually the symptoms of increased intracranial pressure in children occur before there are any focal signs to suggest the location of the lesion. Recurring attacks of headache and vomiting without nausea are the rule. These may occur at intervals of weeks or months with completely symptom-free intervals. Recurring bouts of sudden vomiting without headache are not uncommon. The physician's attention, therefore, may be centered on the gastro-intestinal tract for months or until serious visual disturbance points the way to the correct diagnosis. The visual disturbance may be a diplopia due to sixth nerve paresis from the increased intracranial pressure, or this paresis may proceed to an obvious internal squint before the child complains of it. Failing vision also may reach the point where it is evident to the parents before the child is aware of it. The important thing to remember is to make a fundus examination in any child who is having recurring or continuous attacks of headache or vomiting. Another simple, though later sign of increased intracranial pressure in children is the cracked pot sound on percussion of the skull (Macewen's sign). This is due to the separation of the cranial sutures which are not firmly united in children.

The most common tumor in childhood is the glioma of the cerebellum. These are almost always located in the midline between the two cerebellar lobes and are of two varieties. The cystic astrocytoma is the most benign of the gliomas and yields brilliantly to surgery. The other type, known as a medulloblastoma, is composed of highly undifferentiated cells. It cannot be excised completely but responds better to roentgenotherapy than any other brain tumor. These tumors, because of their midline position, soon obstruct the flow of cerebrospinal fluid from the ventricles and thus cause an obstructive hydrocephalus. Local symptoms are frequently lacking or at most may consist of an instability of gait with frequent falling. One ever-present sign in these cases is anesthesia of the cornea. Nystagmus, ataxia and hypotonia, which are the common

signs of most cerebellar lesions, may be very slight or even absent in these midline tumors.

Another less common tumor in childhood and adolescence is the tumor of the hypophyseal stalk usually referred to as the craniopharyngioma or Rathke's pouch cyst. This tumor arises just above or within the sella turcica from embryonal cell rests left by the outpouching from the primitive nasopharynx which goes to form the anterior lobe of the pituitary gland. Because of pressure on this gland, these tumors usually produce signs of pituitary hypofunction. These children, therefore, are apt to be chubby and dwarfed and the signs of puberty are lacking. In spite of their location in close proximity to the optic nerves and chiasm and because of their cystic nature and slow growth, the resulting loss of vision comes on late and appears gradually. When the cyst has attained sufficient size to compress the third ventricle and thus produce an obstructive hydrocephalus, symptoms of increased intracranial pressure supervene with rapid loss of the remaining vision. These benign epithelial lined cysts are best approached by a frontal craniotomy. Though their total removal is attended by a high mortality due to damage to the surrounding nervous structures, they may occasionally be dissected out with surprising ease. A partial removal is most commonly employed and usually results in a long symptom-free interval. They are not at all sensitive to roentgenotherapy.

Gliomas of the cerebral hemispheres occur in children but they do not produce a syndrome as characteristic as those described above. The meningiomas and neurofibromas rarely occur before the age of maturity.

Glioma of the Cerebral Hemispheres

In adult life, gliomas of the cerebral hemispheres are encountered more frequently than any other type of tumor. These vary in malignancy from the very rapid growing glioblastoma multiforme to the slow growing benign oligoglioma. A fairly typical case history of the former type of tumor is as follows: A healthy active man of 45 years begins to complain of headache. He ignores it for a few weeks but the headaches increase in frequency and severity so that he stays home from work. It is then noted by the family that his memory is impaired and that he is occasionally mildly confused. The symptoms steadily increase in severity and new ones appear. There is numbness or weakness of one side of the body and some blurring of vision. The patient is hospitalized about three months after the appearance of the initial symptom. On examination at this time, the patient is found to be lethargic and confused and he complains of headache when aroused. There is an advanced choking of the optic discs with recent retinal hemorrhages. The neurological signs indicate the location of the lesion fairly definitely. At

craniotomy, the cerebral cortex appears flattened and the intracranial pressure is very high. An incision through the cortex reveals the soft infiltrating growth beneath the surface. Provided with an adequate decompression, the patient improves temporarily after which the intracranial pressure recurs and he dies about four months after operation. This is the type of neoplasm which has gained for brain tumors a most unenviable reputation. It represents about 15 per cent of all intracranial tumors.

The oligoglioma is at the other end of the scale as far as malignancy is concerned. This tumor may cause symptoms for five or ten years and, after a partial removal, the patient may not succumb for another five or ten years. The initial symptom is most commonly a convulsion, usually Jacksonian in character. The convulsions recur at first at long intervals, perhaps years, but steadily increase in frequency and are accompanied by a gradually increasing weakness and spasticity of the extremities affected by the convulsion.* With the appearance of headaches, the patient is referred to the surgeon. From a detailed description of the attacks, it is sometimes possible to localize the lesion accurately without even seeing the patient. This is especially true if the tumor is in the parietal lobe in which case the patient will describe a numbness of the limb preceding the attack. Other aura of immense localizing value are a sudden stench perceived by the patient, indicating an irritation of the uncinate gyrus, or flashes of light in one half of the visual field indicating the opposite visual pathway. Calcium deposits in the oligoglioma are rather frequently visible on the x-ray film and this constitutes another important diagnostic feature.

At operation, this tumor is found near the surface and, due to its firmness, it is readily palpable. It can easily be dissected out on all sides but one. Here it shades off imperceptibly into the white matter. If this area is radically excised, a permanent cure is possible. If it can be done without too great a sacrifice to the patient, it is better to excise the entire affected lobe with the contained tumor.

Between the glioblastoma on the one hand and the oligoglioma on the other, there are many types of gliomas of varying degrees of malignancy and less clear-cut clinical syndromes.

Pituitary Tumor

The pituitary tumor produces a fairly definite symptom complex. This tumor arises from the cells comprising the anterior lobe of the pituitary gland. Histologically and clinically, there are two commonly encoun-

*Convulsions appearing for the first time after the age of 30 are most frequently due to brain tumor and the burden of proof is upon him who would assume otherwise. If the convulsion is followed by a transitory weakness of an arm or leg, the presence of a tumor is particularly indicated.

tered types. The chromophobe adenoma arises from the chromophobe or neutral staining cells and produces a picture of pituitary hypofunction. The acidophilic adenoma arises from the granular cells which take the acid stain and it produces a mixed picture of hyper- and hypofunction. A third and very rare type has been described by Cushing as a basophilic adenoma. This tumor arises from the granular cells which take the basic stain, but it is still questioned by many pathologists and clinicians.

Clinically, the symptoms of pituitary tumor may be divided into the endocrine signs which usually appear early and the pressure signs such as headache and failing vision which appear later. In the most common or chromophobe type, the early symptoms are usually obesity, reduction of libido and in the female, amenorrhea. In the acidophilic type, the symptoms are gigantism if the tumor arises prior to the completion of epiphyseal union, acromegaly, reduction of libido, and, in the female, usually amenorrhea. The former variety is accompanied by a subnormal metabolism and frequently by an increased glucose tolerance. The latter variety is accompanied by an increased metabolism and frequently by elevated blood pressure and decreased glucose tolerance which may amount to a frank diabetes. In neither type is surgical intervention warranted until pressure symptoms intervene. The pressure symptoms are common to the two types and are as follows: Headache which is due presumably to increased pressure within the expanding sella turcica and impairment of vision which becomes manifest when the adenoma has grown upward sufficiently to compress the visual pathways. The most common type of visual loss is a bilateral reduction in visual acuity and a bitemporal hemianopsia due to pressure of the optic chiasm. However, if the lesion expands more rapidly on one side, a unilateral loss of vision and homonymous hemianopsia may result. The optic discs show the pallor of a primary atrophy. In the late stages, somnolence and diabetes insipidus may occur, indicating damage to the hypothalamic structures.

Roentgen examination of the skull in the presence of pituitary tumor always discloses a ballooning out of the sella turcica with the floor pushed downward into the sphenoid sinus. This is not to be confused with the erosion of the clinoid processes produced by tumors arising at a distance from the sella. As stated before, the intracranial pressure is rarely increased in pituitary tumors because serious visual loss usually points the way to the correct diagnosis before the lesions are large enough to cause this condition.

Practically all surgeons agree that these lesions can best be treated by a right frontal craniotomy. The acidophilic type sometimes responds well to roentgenotherapy.

Acoustic Tumor

In the acoustic tumor, a careful chronological history will often establish the diagnosis and almost obviate the necessity for other studies. As these tumors grow on the sheath of the eighth cranial nerve, the initial symptom, as might be expected, is tinnitus accompanied by or followed shortly by increasing deafness. Sometimes there is a brief period of mild vertigo at the onset due to irritation of the vestibular fibers of the eighth nerve. As these fibers are paralyzed by the tumor much earlier than are the auditory fibers, this early vertigo, if present, soon subsides. There then follows a progressive impairment of hearing in the affected ear which becomes complete in a period of months or years. The next symptom is usually a mild unsteadiness of gait which progresses slowly to a marked cerebellar ataxia. During the progression of the ataxia, headache and cranial nerve signs make their appearance. The headache is more commonly suboccipital and frontal and may be confined to the side of the tumor. The symptoms of involvement of the adjacent cranial nerves consist of numbness in the distribution of the trigeminus and occasionally of facial pain which may resemble a true tic doloreaux. Facial weakness as evidenced by a unilateral slowing of the blinking reflex and slight widening of the palpebral fissure is frequently present. As the headache becomes more severe, it is accompanied by forceful vomiting, diplopia and failing vision.

Examination at an early stage in this disease will disclose merely unilateral nerve deafness and lack of response to the labyrinthine tests of Barany on the affected side. Later on, there will appear anesthesia of the cornea, coarse nystagmus especially on looking toward the side of the tumor, Rombergism, staggering toward the affected side, slight facial weakness, internal squint, choked discs and unilateral suboccipital tenderness. Roentgen examination frequently will disclose some erosion of the posterior surface of the petrous bone.

The Meningioma

The meningioma is a benign, encapsulated growth originating in the meninges. It occurs most commonly in the fourth and fifth decades of life and is very rare prior to the third.

Although a preoperative diagnosis of meningioma is not always possible, there are certain findings in the majority of cases which make the diagnosis likely. The following signs and symptoms should lead one to suspect this type of tumor. The onset of symptoms may date back years rather than months as is commonly the case in the more rapidly growing type of lesions. The initial symptom in approximately one-third of the cases is a Jacksonian convulsion. X-ray demonstration of

local thickening or erosion of the skull or actual calcification within the tumor occurs in one-fourth of the cases. A palpable swelling of the overlying scalp occurs in a much smaller proportion. However, the point upon which the differential diagnosis most frequently hinges is the occurrence of a slow growing tumor in a location known to be a favored site of the meningioma. These favored sites in order of their frequency are:

(1) Attached to the lateral wall of the sagittal sinus near the vertex. In this location, Jacksonian convulsions and hemiparesis beginning in the opposite leg are common symptoms.

(2) On the sphenoidal ridge. Here the localizing signs may be meager or absent. The most important evidence is obtained from the roentgen examination which may show erosion of the sphenoidal ridge or dilatation of the middle meningeal groove. Tenderness and fullness in the temporal region is a very suggestive sign.

(3) Over the convexity of the cerebral hemispheres. In this location, the occurrence of Jacksonian convulsions together with roentgen evidence of bony proliferation or erosion is frequent.

(4) From the tuberculum sellae. A meningioma in this location announces its presence when symptoms suggestive of pituitary tumor develop in a middle-aged person, but the roentgenogram fails to show the typical sella picture.

(5) In the cerebellopontine angle. Tumors in this location are difficult to distinguish from acoustic neurofibromas.

(6) In the olfactory groove. Here the story is one of progressive loss of sense of smell, mental symptoms and headache.

(7) On the sheath of the Gasserian ganglion. In this site, the tumor causes trigeminal pain with associated impairment of sensation in the distribution of the fifth nerve.

THE TECHNIC OF A BLOOD EXAMINATION

RUSSELL L. HADEN, M.D.

The first requisite to the study of a blood dyscrasia is a complete and accurate laboratory examination of the blood. The presence of an anemia, leukemia or other disease of the blood may be suggested by the history and physical examination, yet no clinician would hazard a final diagnosis or outline treatment without knowing the results of the laboratory studies. Too often the clinician expresses an opinion based on blood films which are unsatisfactory for examination or on incomplete or inaccurate laboratory data. The selection of the best technical methods is difficult for those who are not constantly studying problems in hematology, although the technical study of blood is simple and requires no complicated apparatus. The methods described here have proven most dependable in our hands.

A routine blood count (red and white cell count, hemoglobin estimation and differential count) is only a starting point for a more complete blood study and should be looked upon largely as a means of determining whether or not a complete blood study is indicated. In every case of anemia the following examinations should be done:

1. Red corpuscle count.
2. Determination of the mass of packed corpuscles.
3. Hemoglobin estimation.
4. Calculation of indices:
    a. Volume index (erythrocyte volume relative to normal) or mean corpuscular volume.
    b. Color index (erythrocyte hemoglobin relative to normal) or mean corpuscular hemoglobin content.
    c. Saturation index (concentration of hemoglobin per unit volume of packed cells relative to normal) or mean corpuscular hemoglobin concentration.
5. White corpuscle count.

6. Study of stained blood film (size, shape, staining reactions and abnormalities of red cells, differential count of white cells, relative number of platelets).

7. Count of reticulocytes.

8. Determination of bile pigment content of the plasma.

These examinations are all necessary and are very easily done. I much prefer to make all examinations, except the study of the stained film, on blood withdrawn from a vein. The blood film alone is made from a drop of blood obtained from the ear lobe or the finger tip. A simple method for the entire examination is as follows: 20 cc. of blood is withdrawn from a vein by means of a syringe, and exactly 10 cc. is run into a 12 or 15 cc. centrifuge tube, containing exactly 2 cc. of 1.4 per cent sodium oxalate solution.[1] This is mixed by inverting and is then spun in a large centrifuge for one hour at 2500 revolutions per minute. The remainder of the blood is added to an ounce bottle containing one drop of a 30 per cent solution of potassium oxalate. The latter specimen is used for the red and white cell count and for the hemoglobin determinations. The examinations are made as indicated below.

1. *Red Cell Count.* One source of inaccuracy in erythrocyte counts is the use of a hypotonic diluting fluid. I prefer to use a 0.9 per cent sodium chloride solution as the diluting agent. Accurate erythrocyte counts require much practice and experience on the part of the technician. It is absolutely necessary that accurately calibrated counting chambers and pipettes be used. These should be certified by the United States Bureau of Standards.

2. *Volume of Packed Red Cells.* This is read off directly from the tube after centrifuging. The volume is recorded as the number of cubic centimeters of cells per 100 cc. of blood, and in per cent of normal. The normal is calculated for each laboratory by determining by means of the centrifuge the number of cubic centimeters of packed cells per 100 cc. of blood in normal individuals with a red cell count of 5 million cells per c.mm. With our present apparatus we have found 45 cc. of cells per 100 cc. of blood to be equal to 100 per cent (Fig. 1).

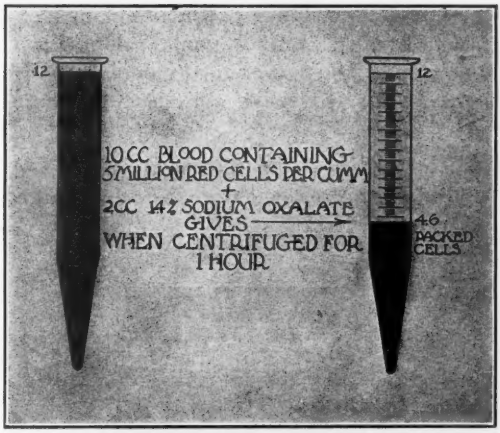

FIG. 1—Pyrex centrifuge tube used for determination of mass of red blood cells.

For any given specimen of blood the number of cubic centimeters of packed cells obtained by centrifuging 10 cc. of blood is read off on the tube and divided by 4.5 cc. (or other figure determined as normal for the 10 cc. of blood).

3. *Hemoglobin Estimation.* Accurate hemoglobin determinations may be made quite easily by the oxygen capacity method, using the Van Slyke apparatus, or by one of the iron methods. Such procedures are not practical, however, in routine clinical work. The exact number of grams of hemoglobin present in any given blood is of no great clinical importance. It is exceedingly important, however, to determine the hemoglobin content relative to normal. This can be done simply if a hemoglobinometer reading directly in grams is used for the determination. The new Sahli, the new Dare, the Bausch and Lamb-Newcomer, the Klett, the old Miescher-von Fleischl, and the Haden-Hausser[2] instruments, all read in grams although no two give the same reading on the same specimen of blood. This makes little difference if everyone in his own laboratory determines for the instrument used the average number of grams of hemoglobin per 100 cc. of blood in normal individuals with a red cell count of 5 million per c.mm., and takes this as 100 per cent. The results are then always reported, not in the absolute number of grams per 100 cc. but in per cent of normal. In normal individuals the color index is always 1.00 within the limits of error. By this method the precentage of hemoglobin for a given specimen of blood would always be the same in all laboratories although the actual number of grams of hemoglobin determined would be different in each.

In our laboratories the Haden-Hausser hemoglobinometer (Fig. 2) which reads only in grams is used routinely and 15.4 grams of hemoglobin is taken as 100 per cent. The new clinical model of the Haden-Hausser hemoglobinometer is less expensive and gives accurate readings in grams.

4. *Calculation of Indices.* By the methods outlined we are able to determine accurately the red cell count and the packed cells in per

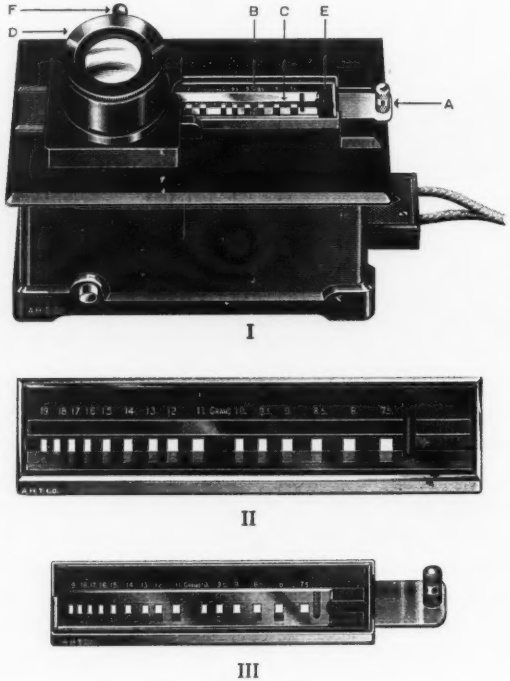

FIG. 2—Hadden-Hausser hemoglobinometer (laboratory model). I. Complete instrument. A, movable carrier; B, comparator slide; C, cover glass; D, reading microscope; E, wedge-shaped channel; F, light shutter. II. Comparator slide. III. Comparator slide with cover glass in metal holder.

cent of normal, packed cells (normal equals the number of cubic centimeters of packed cells found in 100 cc. of normal blood with a red cell count of 5 million) and the hemoglobin in per cent of normal hemoglobin (normal equals the number of grams of hemoglobin found in 100 cc. of normal blood with a red cell count of 5 million). Suppose for a given laboratory a specimen of normal blood with a red cell count of 5 million per c.mm. yields 46 cc. of packed cells per 100 cc. on

centrifuging with an isotonic anticoagulant for one hour at 2500 revolutions per minute, and contains 15 grams of hemoglobin per 100 cc. and a specimen of anemic blood with a red cell count of 1.5 million yields 18.4 cc. of packed cells, and contains 6.0 grams of hemoglobin, then:

(a) The volume index (volume of mean cell relative to normal)

$$\text{of the normal blood} = \frac{\dfrac{\text{Number of cc. of packed cells found per 100 cc.}}{\text{Normal number of cc. of packed cells per 100 cc.}}}{\dfrac{\text{Number of red cells found}}{\text{Normal number of red cells}}} = \frac{\dfrac{46}{46}}{\dfrac{5{,}000{,}000}{5{,}000{,}000}} = 1.00$$

$$\text{of the anemic blood} = \frac{\dfrac{18.4}{46}}{\dfrac{1{,}500{,}000}{5{,}000{,}000}} = 1.33$$

The mean corpuscular volume[3] (the volume of the average red corpuscle in cubic microns) is calculated by dividing the volume of packed cells per 100 cc. by the number of cells contained in 100 cc. of blood. The result may be calculated in cubic microns by multiplying by 2 the volume of packed cells per 100 cc. per 5,000,000 cells.

Thus the mean corpuscular volume of the normal blood = 46 x 2 = 92 cubic microns; of the anemic blood $= \dfrac{18.4}{\dfrac{1{,}500{,}000}{5{,}000{,}000}} \times 2 = 61.3 \times 2 = 123$ cubic microns

(b) The color index (amount of hemoglobin per cell relative to normal)

$$\text{of the normal blood} = \frac{\dfrac{\text{Number of grams of hemoglobin found per 100 cc.}}{\text{Normal number of grams of hemoglobin}}}{\dfrac{\text{Number of cells found per c.mm.}}{\text{Normal number of red cells per c.mm.}}} = \frac{\dfrac{15}{15}}{\dfrac{5{,}000{,}000}{5{,}000{,}000}} = 1.00$$

$$\text{of the anemic blood} = \frac{\frac{6.0}{15.0}}{\frac{1{,}500{,}000}{5{,}000{,}000}} = 1.33$$

The mean corpuscular hemoglobin[3] (the hemoglobin content of the average red corpuscle in micromicrograms) is calculated by dividing the hemoglobin in grams per 100 cc. of blood by the number of cells contained in 100 cc. of blood. It is simply calculated in micromicrograms by multiplying by 2 the number of grams of hemoglobin per 100 cc. of blood per 5 million cells.

Thus the mean corpuscular hemoglobin of the normal blood = 15.0 x 2 = 30

$$\text{micromicrograms of the anemic blood} = \frac{6.0}{\frac{1{,}500{,}000}{5{,}000{,}000}} \times 2 = 20 \times 2 = 40 \text{ micromicrograms}$$

(c) The saturation index (amount of hemoglobin per unit volume of cell relative to normal)

$$\text{of the normal blood} = \frac{\dfrac{\text{Number of grams of hemoglobin found in 100 cc.}}{\text{Normal number of grams of hemoglobin per 100 cc.}}}{\dfrac{\text{Number of cc. of packed cells found per 100 cc.}}{\text{Normal number of cc. of packed cells per 100 cc.}}}$$

$$= \frac{\frac{15}{15}}{\frac{46}{46}} = 1.00$$

$$\text{of the anemic blood} = \frac{\frac{6}{15}}{\frac{18.4}{46.0}} = 1.00$$

The mean corpuscular hemoglobin concentration[3] (the concentration of the hemoglobin in per cent per unit volume of cells) is calculated by dividing the number of grams of hemoglobin per 100 cc. of blood by the number of cubic centimeters of packed cells per 100 cc.

Then the mean corpuscular hemoglobin concentration in the normal blood $= \frac{15}{46} = 32.6$ per cent, in the anemic blood $= \frac{6.0}{18.4} = 32.6$ per cent.

The calculation of the different indices is facilitated by the use of a nomogram (Fig. 3).

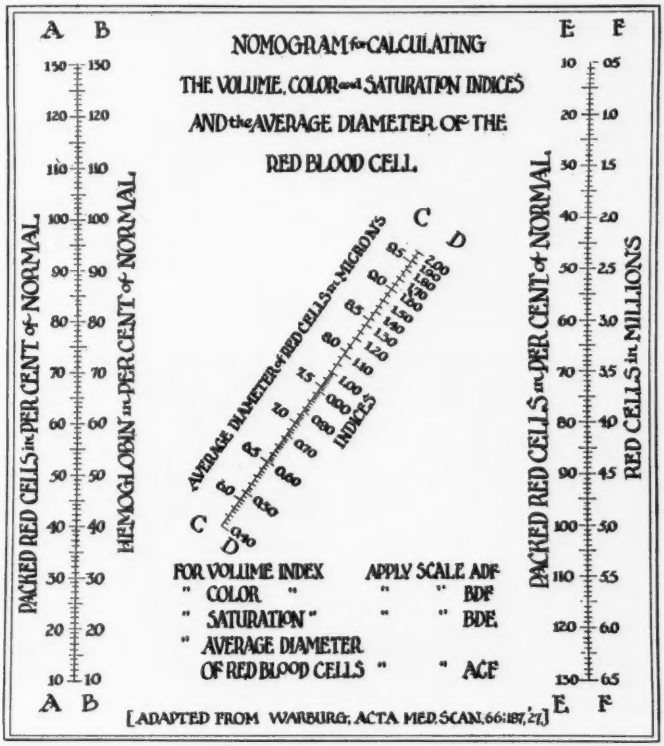

FIG. 3—Nomogram for calculating indices from red cell count, hemoglobin in per cent of normal and packed red cells in per cent of normal. The mean diameter of the red blood cells can also be calculated.

5. *White Corpuscle Count.* This is subject to fewer errors and greater variation than is the red cell count but should be done equally carefully.

6. *Preparation of Stained Film.* In many laboratories blood films are made only on slides. For the study of the morphology of the red cells, for reticulocyte counts and for examinations for parasites, such films are satisfactory. For an accurate differential count, for determining the relative number of platelets, and for studying the morphology of the white cells, films made on cover glasses are far preferable. The technic of a blood examination is certainly not mastered until one can make satisfactory cover glass preparations. These are easily made if certain precautions are observed. I find no difficulty in having the best of preparations made by efficient technicians.

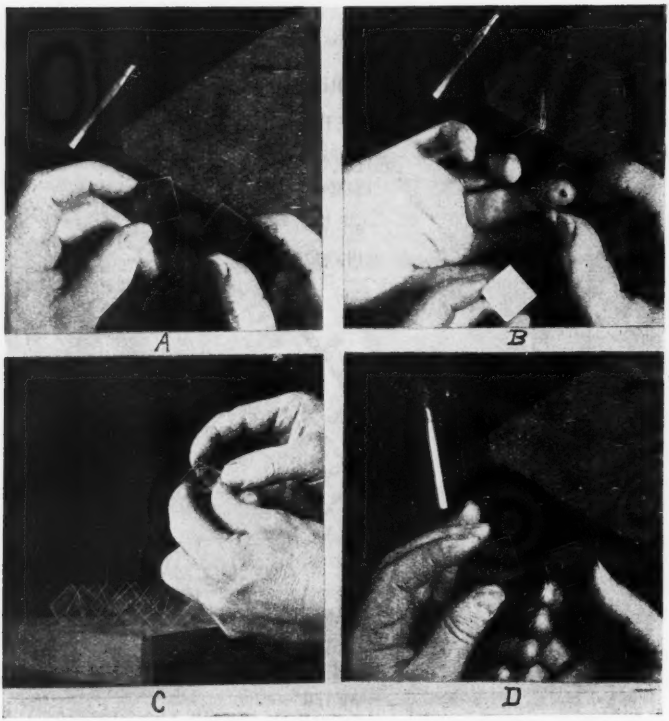

FIG. 4—The preparation of blood films by the cover glass method. A. a cover glass (⅞ inch square No. 2) is grasped at the adjacent corners with the thumb and forefinger of each hand; B. the drop of blood is touched with the cover glass held in the right hand; C. the cover glass carrying the drop of blood is quickly placed parallel on the cover glass held in the left hand; D. cover glasses are then drawn apart with a sliding motion, care being taken to keep them parallel. The films are allowed to dry in air and are then ready for staining. The drop of blood must be globoid on the finger tip and just large enough to cover the cover glass when properly spread. (From Haden—*Clinical Laboratory Methods.)*

The most satisfactory cover glasses are No. 2, ⅞ inch square of good manufacture. They must be absolutely clean and free from dust. Some cleaning solution such as a concentrated acid or bichromate acid mixture is often employed. The best method of cleaning is to scrub them with some grit-free scouring powder such as Dutch Cleanser. The hands are thoroughly washed, a number of cover glasses placed in the palm of one and the scouring powder and a small amount of water added. The glasses are then well scrubbed with the palm of the other hand, using a rotary motion. They are rinsed with distilled water, placed in alcohol, dried with a clean, lint-free cloth, and stored in boxes. Just before use they are brushed off with a camel's hair brush and placed on edge in a block of wood or in the top of a box.

We usually make a number of slits in the top of a 20 cc. syringe box and keep in the box an automatic lancet, the box of cleaned cover glasses, a camel's hair brush, cotton gauze and a small bottle of alcohol, thus providing everything needed for making blood films.

In making the films, a clean and dust-free cover glass is grasped at the adjacent corners with the thumb and forefinger of each hand and the drop of blood on the finger tip is touched with the cover glass held in the right hand (Fig. 4). The cover glass carrying the drop of blood is quickly pressed parallel to the cover glass held in the left hand. The blood spreads by capillary attraction. As the spread is completed, the cover glasses are drawn apart with a sliding motion, care being taken to keep them parallel. The films are allowed to dry in air and are then ready for staining. The finger is punctured with an automatic lancet, since the depth of the puncture wound can be regulated best in this manner. The drop of blood must be globoid on the finger tip and just large enough to cover the cover glass when properly spread.

Staining the Blood Film. The films are best stained on a small stand made by nailing a row of corks to a wood block (Fig. 5). Wright's stain

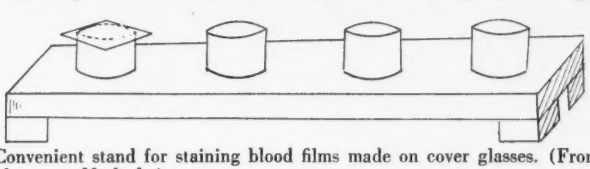

FIG. 5—Convenient stand for staining blood films made on cover glasses. (From Haden—*Clinical Laboratory Methods.)*

is the most satisfactory one for routine use. Only chemically pure, acetone-free methyl alcohol such as Merck's Blue Label should be employed in making the staining solution. Cover the blood film with about 10 drops of stain and after one minute add an equal number of drops of distilled water. Very often preparations made in this manner are too blue, due to an excess of alkali in the stain. The simplest way to correct an excess of alkalinity is by adding a phosphate buffer solution. The optimum amount of buffer solution to be added must be determined by trial. Usually the most satisfactory stains are made by adding 3 drops of a phosphate buffer solution with a PH equal to 6.4 and 8 to 10 drops of distilled water. If the staining solution is very alkaline, only the buffer solution is used. Let stand for four to five minutes. The phosphate buffer solution with PH equal to 6.4 is made as follows:

Primary potassium phosphate (KH_2PO_4)	6.63 gm.
Anhydrous secondary sodium phosphate ($Na_2H\ PO_4$)	2.56 gm.
Distilled water to make	1000.00 cc.

The stained films are mounted film side down in neutral gum damar solution. A rather thin solution of gum damar in chemically pure zylol is made, calcium carbonate is thoroughly mixed with it and the solution placed in the window in the sunlight for several weeks. After the calcium carbonate has completely settled out, the solution is poured off and placed in a warm place until it has evaporated to the proper consistency. The gum damar thus made is neutral, does not darken with age, and does not cause fading of the stain.

7. *Count of Reticulocytes.* The reticulocytes may be stained with brilliant cresyl blue in a number of different ways. Often a film of cresyl blue is prepared on cover glasses and the blood film made on this. We prefer the following technic: A drop of a saturated solution of brilliant cresyl blue in alcohol is placed on a porcelain drop plate (Fig. 6) and allowed to evaporate to dryness. One drop of the blood

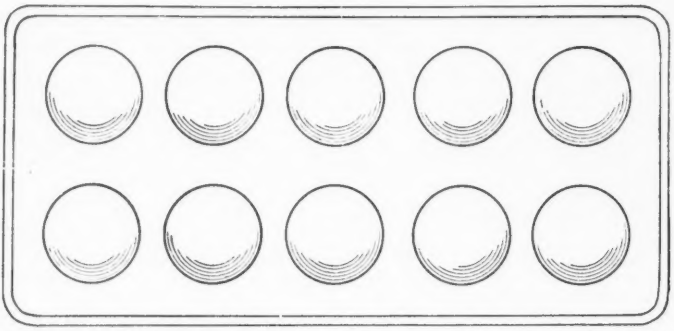

FIG. 6—Porcelain mixing plate for use in blood grouping. (From Gradwohl and Blaivas—*Blood and Urine Chemistry.)*

taken from the centrifuge tube prepared for the determination of the red cell volume is mixed with the stain. This is taken up with a pipette. Films are prepared on cover glasses and counterstained with Wright's stain.

If only a reticulocyte count is to be made, a drop of blood from the finger tip is taken up with a capillary, mixed with the dried stain in the drop plate, and blood films made from the mixture.

8. *Determinations of Bile Pigment Content of the Blood Plasma.* The bile pigments are easily and satisfactorily estimated as the icterus index. I use the method suggested by Murphy.[4] For the color comparison, a series of standards are prepared from various dilutions made from a 1:100 solution of potassium bichromate to correspond with varying icterus index figures as shown in Table I.

TABLE I

Dilution	*Corresponding Icterus Index*	*Dilution*	*Corresponding Icterus Index*
1:10,000	1	1:500	20
1: 5,000	2	1:400	25
1: 2,000	5	1:200	50
1: 1,000	10	1:133	75
1: 666	15	1:100	100

The solutions are kept in a rack in small test tubes 10 mm. in diameter (Fig. 7). One or two cubic centimeters of the supernatant

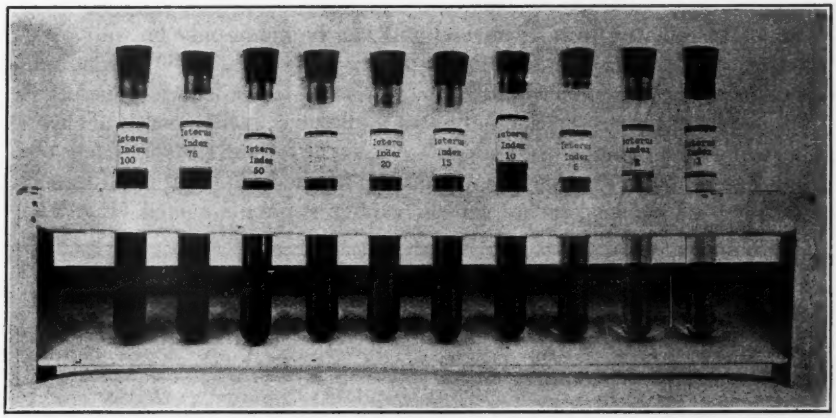

FIG. 7—Set of bichromate standards for estimating the icterus index.

plasma is pipetted from the centrifuge tube after spinning into a similar test tube and compared with the bichromate standards. The figure corresponding to the dilution which matches the serum is the icterus index of the serum. A correction is made for the dilution with oxalate. The normal icterus index is 4 to 6. To avoid clouding, blood should be taken when the patient is fasting. In preparing the dilutions of potassium bichromate, 2 drops of concentrated sulphuric acid should be added to each 500 cc. to prevent fading.

To Recapitulate. Twenty cubic centimeters of blood have been taken from the patient's vein and blood films have been made from the finger tip. Ten cubic centimeters of blood have been mixed with isotonic sodium oxalate. Before centrifuging, films for a count of the reticulocytes have been made from a drop of the oxalated blood. After centrifuging, the volume of red cells has been read off and the icterus index has been determined on the supernatant plasma. Red cell and white cell counts have been made on the specimen to which a

drop of potassium oxalate has been added. The blood film has been stained and examined and the indices have been calculated from the data obtained above. A complete examination has thus been made with a minimum expenditure of time and trouble. Tests other than those outlined above may be indicated. The more common one of definite value is a special study of white cells.

a. For Maturity: Numerous classifications to indicate the maturity of the polymorphonuclear cells, based on a study of the nucleus have been suggested (Arneth, Schilling, Cooke and Ponder, Pons and Krumbhaar). In my opinion the most satisfactory and practical classification is the separation of the polymorphonuclear neutrophiles into two groups, filamented and nonfilamented, as suggested by Farley, St. Clair and Reisinger.[5] Such counts can be made only on well prepared and properly stained blood films on cover glasses. One hundred polymorphonuclear neutrophiles are counted. Cells in which the lobes of the nucleus are connected only by a thin strand or filament of nuclear material are counted as filamented cells. If there is any band of nuclear material except this chromatin filament connecting different parts of the nucleus, such a cell is counted as nonfilamented (Fig. 8).

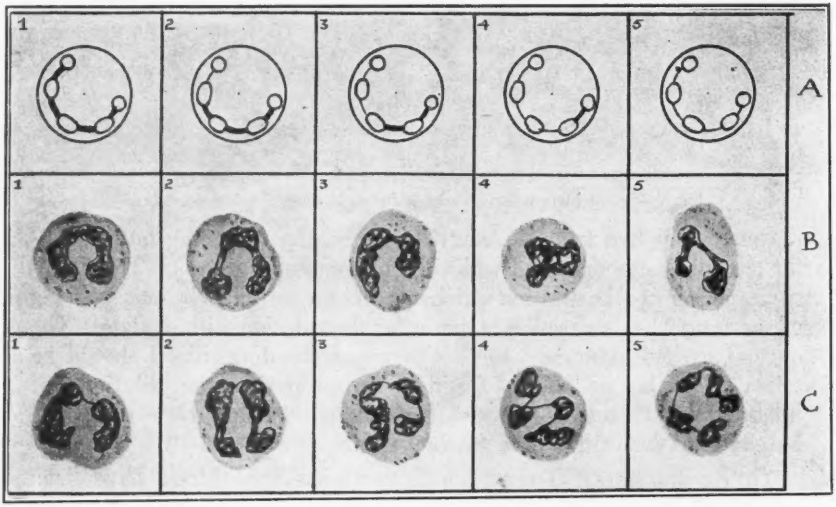

FIG. 8—A diagram to illustrate different types of nuclei in polymorphonuclear neutrophilic cells. 1. polymorphonuclear with nucleus of five lobes connected by thick bands of nuclear tissue. The nucleus shows five distinct masses but since the connecting threads are thick, the cell is designated nonfilamented. 2, 3, 4, 5, polymorphonuclears in which two or more lobes are connected only by a filament. These four cells are all designated "filamented" polymorphonuclears. B. 1, 2, 3, 4, 5, nonfilamented polymorphonuclears. In each cell the lobes of the nucleus are connected by thick threads. C, 1, 2, 3, 4, 5, filamented polymorphonuclears. In each cell two or more lobes are connected only by a filament of nuclear tissue. (Adapted from Cooke and Ponder's—*The Polynuclear Count.)*

If 100 polymorphonuclear cells are counted, not more than 25 per cent should be nonfilamented. If only 100 white cells of all types are counted, not over 16 per cent of the neutrophiles should be nonfilamented.

Any irregularity in size and staining reactions of the granules should should be noted, since such changes are a good index of the degree of toxicity and may be equally important as variations in maturing of the nucleus.

b. For Oxidase Content: This is of value in differentiating cells of the lymphocyte and bone marrow series. I think the Washburn method gives the best preparations.

Washburn's Method. 1. Thin smears should be made, allowed to dry and stained within three to four hours.

2. Flood the smear with 10 drops of solution No. 1 and allow to stand for one to one and one-half minutes.

SOLUTION No. 1

Benzidine base	0.3 gm.
Basic fuchsin	0.3 gm.
Sodium nitroprusside (sat. aq. sol.)	1.00 cc.
Ethyl alcohol (95 per cent)	100 cc.

Dissolve the benzidine and fuchsin in the alcohol in order named. Then add the nitroprusside solution. A slight precipitate may form at the bottom of the flask but does not interfere with the staining qualities. This solution will keep for eight to ten months.

3. Add 5 drops of solution No. 2 without pouring off No. 1 and allow to stand three to four minutes.

SOLUTION No. 2

Hydrogen peroxide	5 to 6 drops
Tap water	25 cc.

This solution will keep for about two days.

4. Wash thoroughly with tap water (one-half to one minute).

5. While still wet, flood with 95 per cent ethyl alcohol and allow to stand three to four minutes, or until completely decolorized (i.e., when there is no more pink visible to the naked eye).

6. Wash thoroughly with tap water and dry.

7. Flood with 8 drops of Wright's stain and allow to stand for two to three minutes.

8. Add 14 drops of tap water (one and one-half times as much water as Wright's stain) and allow to stand for twenty to forty-five minutes. Most normal and many abnormal bloods will stain well in twenty to twenty-five minutes but certain abnormal bloods, particularly the leukemic bloods, require thirty-five to forty minutes.

9. Wash briefly with tap water, flood with 95 per cent alcohol for three to five seconds and immediately wash with tap water for ten to fifteen seconds.

10. Dry and examine.

The peroxidase granules are black. The nuclei and the cytoplasm of the cells are identical with those seen in a Wright stain.

c. Jenner-Giemsa Stain for Special Study of Leukocytes: The films stained by Wright's method are satisfactory for most purposes. The Jenner-Giemsa stain brings out beautifully the finer details of nuclear and the other cell structures. In leukemia especially, such preparations are valuable. They are made as follows:

The cover glass preparation is covered with Jenner's stain for three minutes, and an equal number of drops of distilled water added. After one minute, the stain is washed off. The cover glass is then placed with the film down in a watch glass. The Giemsa stain (15 drops of the stock Giemsa solution to 10 cc. of distilled water) is run into the watch glass from the side and left for from ten to fifteen minutes. Wash, dry, and mount in neutral gum damar.

Special Examinations Indicated in Hemorrhagic Diseases and Other Conditions

1. *Platelet Count.* An excellent idea of the relative number of platelets may be gained from an examination of a properly made cover glass preparation. If the number seems diminished, a count should be done. The Rees-Ecker method is a very satisfactory one. A small amount of diluting fluid (sodium citrate, 3.8 grams, formalin, 0.2 cc., brilliant cresyl blue, 0.1 gram, distilled water, 100 cc.) is drawn into the bulb of the diluting pipette to moisten the capillary. The blood is then drawn up to the 0.5 mark and the bulb filled with the diluting fluid. The counting and calculation is done as for a red cell count.

2. *Determination of Fragility of Erythrocytes.* The method described for this by Giffin and Sanford[7] is a simple and satisfactory one (Fig. 9). Twelve Wassermann tubes are set up in a rack and num-

FIG. 9—Method for determination of fragility of red blood cells. One drop of whole blood is added to each tube of hypisotonic solution. (After Giffin and Sanford.)

bered 25 to 14 from left to right, with a capillary pipette run into each tube, the number of drops of an accurately made solution of 0.5 per cent sodium chloride being indicated by the figure on the tube. Distilled water is added by means of the same pipette to make the total number of drops of an accurately made solution of 0.5 per cent sodium chloride indicated by the figure on the tube. Distilled water is added with the same pipette to bring the total number of drops in each tube up to 25. Blood is withdrawn from a vein by means of a dry sterile syringe and one drop run into each tube. The tubes are allowed to stand at room temperature for one hour or more. The dilution in which there is just a slight tingeing of the supernatant fluid due to laking of a few of the least resistant corpuscles is noted as the point of initial hemolysis. Reading from left to right, complete hemolysis is indicated in the first tube in which no corpuscular residue is evident by shaking the tube.

The percentage of sodium chloride in any tube is calculated by multiplying the number on the tube by 0.02. Normal blood shows intense hemolysis in 0.42 or 0.38 per cent sodium chloride solution, and complete hemolysis in 0.36 to 0.32 per cent.

3. *Determination of Coagulation Time.* It is a waste of time to determine the coagulation time on a drop of blood obtained by piercing the skin. The method suggested by Lee and White[8] is a satisfactory one for clinical use. Blood is withdrawn from a vein with a syringe in which the space between the end of the plunger and the needle is filled with salt solution, and one cubic centimeter is run into each of 3 small Wassermann tubes 8 mm. in diameter. The tubes should be scrupulously clean and washed with salt solution just before use. After standing for three minutes, a tube is rotated endwise every thirty seconds, and that point at which the blood no longer flows from its position but maintains its surface contour when inverted is taken as the end point. Normal blood coagulates by this method in five to eight minutes.

4. *Bleeding Time.* This is easily and quickly done by the method of Duke.[9]

A small incision is made in the finger or in the lobe of the ear and at half minute intervals the blood is blotted up with smooth filter paper. The cut should be such that the diameter of the first blot is about 2 cm. without any squeezing. Each blot represents the flow of blood in a half minute. The bleeding time is the total duration of the hemorrhage and varies from 1 to 3 minutes in normal individuals.

5. *Clot Retraction.* A few cubic centimeters of blood are run into a Wassermann tube and allowed to stand at room temperature without being disturbed. Normally the clot retracts and expresses blood serum in one hour. If there is a deficiency in platelets, the clot does not retract.

The following form is a convenient one on which to report the results of the examination.

THE TECHNIC OF A BLOOD EXAMINATION

BLOOD REPORT

Name: Date:
Case No: Service:

1. RED BLOOD CELLS:
   1. Number per c.mm.—
   2. Size in stained preparation—
   3. Shape in stained preparation—
   4. Color in stained preparation—
   5. Regeneration forms:
      a. Nucleated red cells—
      b. Basophilia: punctate or diffuse—
      c. Nuclear particles—
   6. Fragility: hemolysis begins in % : complete in % sodium chloride (normal)
   7. Reticulocyte count—
2. VOLUME OF PACKED RED BLOOD CELLS % of normal (cc. per 100 cc.)
3. VOLUME INDEX (Mean corpuscular volume = cubic microns)
4. HEMOGLOBIN % of normal (gm. per 100 cc. with hemoglobinometer)
5. COLOR INDEX (Mean corpuscular hemoglobin = micromicrograms)
6. SATURATION INDEX (Mean corpuscular hemoglobin concentration = per cent)
7. WHITE BLOOD CELLS:
   1. Number per c.mm.—
   2. Differential count:
      Neutrophiles— % Eosinophiles— % Basophiles— %
      Lymphocytes— % Monocytes— %
      Nonfilamented neutrophiles— % (normal 6-16%)
   3. Presence of abnormal forms:
      (a) Myelocytes— (c) Lymphoblasts
      (b) Myeloblasts— (d) Fragile leukocytes
      (e) Toxic neutrophiles
8. BILE PIGMENTS IN PLASMA:
   (a) Icterus index (Normal 0.5 to 2 units)
   (b) Units (van den Bergh) per 100 cc. (Normal 4 to 6)
9. PLATELETS per c.mm.
10. COAGULATION TIME (method)
11. REMARKS
12. LABORATORY DIAGNOSIS:

Name of Examiner.....

RUSSELL L. HADEN

The Laboratory Classification of Anemia on the Basis of Volume and Hemoglobin Content of the Mean Red Cell

The laboratory classification of anemia has always been unsatisfactory. A rough differentiation into primary and secondary types is very frequently used. The anemias having a color index greater than 1.00 are usually classified as primary and those having a color index of 1.00 or less as secondary. Hampson and Shackle[10] first suggested the classification of anemias on the basis of cell size, using the terms "megalocytic" and "nonmegalocytic." Wintrobe[11] suggested four groups: (1) macrocytic, (2) normocytic, (3) simple microcytic, and (4) hypochromic. The most logical laboratory classification is based on all three variants of the erythrocyte, namely, number, size, and hemoglobin content. The following terms may well be employed to indicate variations which have been observed in these factors.

Number
- Hypercythemic = red cell count > normal
- Normocythemic = red cell count within normal limits
- Hypocythemic = red cell count < normal

Volume

Macrocytic = mean corpuscular volume > normal (VI > 1.10)
Normocytic = mean corpuscular volume = normal (VI = 0.90-1.10)
Microcytic = mean corpuscular volume < normal (VI < 0.90)

Hemoglobin Content

Hyperchromic = Mean corpuscular hemoglobin > normal (C I > 1.10)
Normochromic = Mean corpuscular hemoglobin = nomal (C I = 0.90-1.10)
Hypochromic = Mean corpuscular hemoglobin < normal (C I < 0.90)

All the different types of anemia which may occur from this standpoint are:

- Normocythemic
  - Normocytic and hypochromic
  - Microcytic and hypochromic
- Hypercythemic
  - Normocytic and hypochromic
  - Microcytic and hypochromic
- Hypocythemic
  - Macrocytic and hyperchromic
  - Macrocytic and normochromic
  - Macrocytic and hypochromic
  - Normocytic and normochromic
  - Normocytic and hypochromic
  - Microcytic and hypochromic

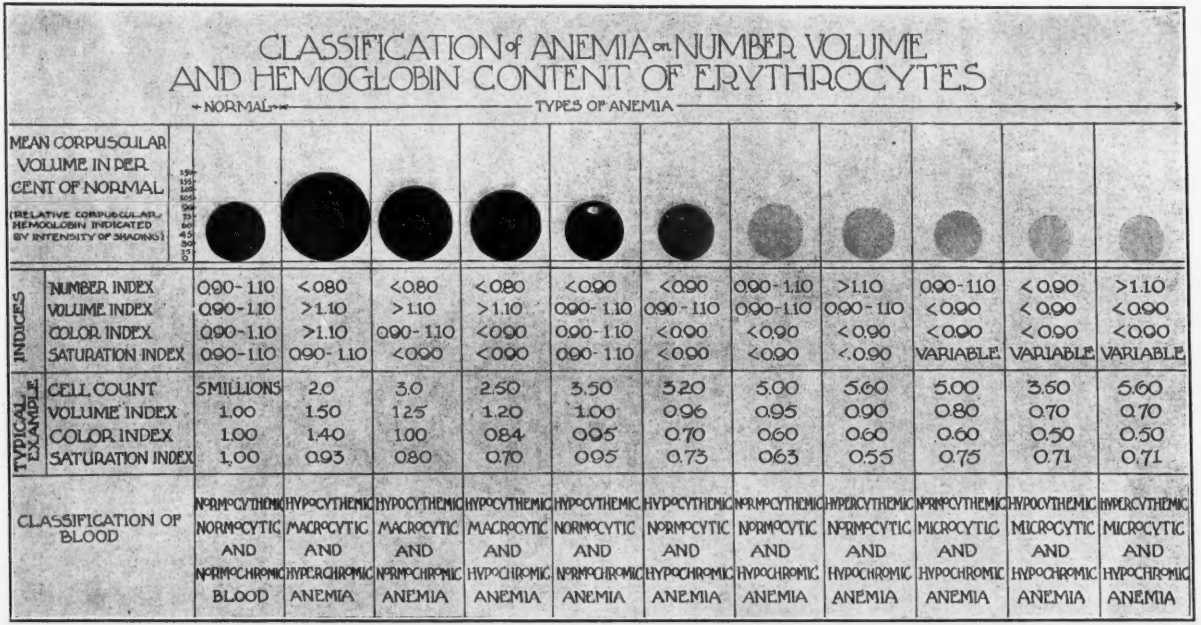

FIG. 10—Showing classification of anemias on number, volume and hemoglobin content of red blood cells.

These types of anemia are illustrated in Fig. 10. The circles indicate relative volume, not diameter, and the intensity of color indicates the relative hemoglobin content. A typical example of each type of anemia is given. Every anemia should be thought of in terms of number, volume and hemoglobin content of the average erythrocyte, and every case should be classified on such criteria. An anemia with a red cell count of 3.50 millions, a volume index of 0.75 and a color index of 0.65 is reported as a hypocythemic, microcytic and hypochromic anemia rather than simply as "secondary" anemia. Likewise an anemia with a count of 2 millions and a volume and color index of 1.50 is recorded as hypocythemic, macrocytic and hyperchromic rather than "primary."

Summary

I have tried to emphasize the need for an accurate and complete examination of the blood in studying hemotologic problems. Any clinician who has had the opportunity of utilizing such an examination will never be satisfied with any other kind. A complete blood study may be made quickly and simply in a well equipped laboratory.

I have indicated one satisfactory technic for each of the tests suggested, although others may be equally satisfactory. One good method should be used until it is thoroughly mastered.

Only with such laboratory data can an accurate knowledge of the blood dyscrasias be gained.

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A CONSIDERATION OF THE DEFICIENCY FACTOR IN DISEASES OF THE GASTRO-INTESTINAL TRACT*

C. L. Hartsock, M.D.

Four factors are operative in the production of deficiency disease.

1. The diet may be deficient in the food elements.

2. The diet may be sufficient, but a deficiency may exist because digestion has not prepared the food properly for utilization by the body.

3. The diet may ordinarily be sufficient but a relative deficiency may exist because of poor absorption from the gastro-intestinal tract, or from rapid loss of food substance through prolonged vomiting or diarrhea.

4. In some conditions such as pregnancy and hyperthyroidism, an increased demand by the body may cause a relative deficiency.

When it was recognized that certain diseases were caused by the lack of certain unknown substances in the diet, the first factor in the production of deficiency disease was self-evident. The recognition of this important fact immediately opened the large problem of what diseases are due to deficient diet, what substances are necessary to the human economy, what are the sources of these substances in natural foods, can they be artificially prepared and what quantity of these substances is necessary to prevent disease. Many of these problems have been answered, and today it is recognized that many diseases are definitely due to deficiency, many more are suspected, and undoubtedly others will eventually be added to this group. The general public has been so enlightened by what has been learned about the nature, source and quantity of these substances which are necessary to prevent disease, that, barring economic factors, it is rare to find the diet of the normal individual deficient in the known needed substances. But if for any reason, the individual subjects himself, or it is necessary for his physician to subject him to a dietary regime, certain precautions then become necessary to prevent a state of deficiency.

The whole problem, however, became much more interesting and complicated with Castle's discovery that pernicious anemia was a deficiency disease, not because of the usual conception of a deficient diet, but because the gastric secretion was deficient in an unknown digestive principle which, in the normal person, produced a substance in the digestion of food that was essential to the proper maturation of the red blood cell in the bone marrow. This work led to the second factor in the conception of deficiency disease; namely, that disease

*Read before the annual meeting of the American Therapeutic Association, June 12, 1935, Atlantic City, N. J.

of the gastro-intestinal tract may cause a deficiency state even in the presence of a normal diet.

Observations of patients who were treated for pernicious anemia by the oral route soon led to the discovery that absorption from the gastro-intestinal tract was also a factor in the production of deficiency disease. Many patients would not respond with extremely large amounts of liver by mouth, but would make a normal response when liver was administered parenterally. This could lead to only one conclusion; namely, that the gastro-intestinal tract was not absorbing the essential substance present in the liver, and thus factor number three was added to complicate the picture of deficiency disease. With the renewed interest in deficiency disease occasioned by these observations, another factor was soon recognized. Diseases exactly similar to known dietary deficiency disease were observed in patients who suffered from long continued vomiting or diarrhea. The explanation was soon apparent, and it was seen that these conditions were the same as dietary deficiency with the exception that the deficiency resulted from such rapid loss of food substance that absorption could not take place.

The fourth factor—that of increased demand, lies more in the realm of theory than of fact. It appears, however, that in the presence of pregnancy, infections, hyperthyroidism, etc., more of the protective substances are necessary than under normal conditions.

It is apparent, therefore, that in every disease and functional disturbance of the gastro-intestinal tract, one or all of these factors may be in operation. If a careful search is made, evidence of mild and sometimes of severe deficiency disease is observed frequently enough in these patients that I believe a deficiency state should be considered a potential complication of all chronic gastro-intestinal diseases. The responsibility for the occurrence of such complications will rest largely upon the physician to whom these patients come for treatment. The ease with which most deficiency states can be prevented emphasizes the responsibility of the physician to anticipate their possible development. In order to anticipate and prevent these deficiency diseases by means other than the indiscriminate and expensive practice of administering the essential foods in a wholesale manner, the following questions become pertinent:

1. What are the most important essential food elements, what is the best source of these substances, the best mode of administration, the quantity needed for cure and continued prevention of deficiency diseases?

2. What diseases related to the gastro-intestinal system and the diets commonly used in their treatment especially predispose to deficiency states?

3. What deficiency diseases are most likely to occur in the presence of such diseases and diets, and what food elements should be supplied liberally for protection?

4. What are the earliest symptoms and signs that one should look for to detect incipient deficiency disease?

5. What examinations should be done that will give helpful clues to preventive therapy?

6. What consideration should one give to possible hypervitaminosis and the expense of supplying unnecessary and excessive vitamins?

7. What may we learn about still unknown deficiency diseases by careful observation of patients with chronic gastro-intestinal disease?

It is not the purpose of this paper to take up these points individually and to discuss them fully. They will be touched upon briefly, but other sources should be consulted for more detailed information.

In a consideration of the diseases of the gastro-intestinal tract which predispose to deficiency disease, it will not be necessary to consider them individually, but they can be grouped according to their symptomatology, pathology and customary treatment.

In one such group, a common finding is hyperacidity. Here we find such conditions as gastric and duodenal ulcer, disease of the gallbladder, nervous indigestion and irritable colon. No matter what the difference in the details of treatment, a special diet is prescribed and treatment with alkalies is instituted in practically all cases. If the condition is severe and chronic, the diet may necessarily be rather strict and long continued. Fresh fruits and vegetables, especially citrus fruits, are forbidden. This may lead to a deficiency of vitamin C. Frequently I have seen soft, spongy, bleeding gums develop in these patients, and these responded promptly to treatment with an increase of vitamin C. Although a serious scorbutic condition probably would never develop, these patients should be protected against this mild deficiency, because other still unknown conditions may result from a deficiency in vitamin C. Dental caries has been attributed by one school of observers to a deficiency in vitamin C. Adequate protection can be given without difficulty to the patient, and this is usually best done by giving lemon juice well diluted in warm water. Orange juice and tomato juice can be taken in small amounts, but amounts sufficient for protection are likely to produce digestive symptoms.

Vitamin A usually is not considered a potential deficiency in this group because butter and cream are supplied in large amounts. However, where alkalies are used extensively and for a long period of time,

the urine becomes strongly alkaline, and this causes precipitation of crystals in the urine. Deficiency of vitamin A results in keratinization of the epithelium in various parts of the body including the renal pelvis and ureters. If the epithelium of the urinary system, especially of the renal pelvis, is not in perfect condition, these crystals may collect on the impaired epithelium and produce stones. Higgins has emphasized the parts played by acidification of the urine and vitamin A in the solution of urinary calculi. O'Conner in discussing Higgins' paper was favorably impressed by the use of vitamin A in the prevention of urinary calculi in patients for whom alkaline therapy had been prescribed, and in whom he had noticed previously a very high incidence of stones. This evidence strongly suggests the need for a high vitamin A intake in this group of patients.

Special consideration of the vitamin and mineral content of the diet must be given in that large and heterogeneous group of patients who have anorexia or who eat very little for one reason or another. The appetite is impaired by so many conditions that only a few of the more common ones can be mentioned. These are the general systemic diseases, especially the chronic infections; the asthenic states due to nervous and physical exhaustion; the psychic disorders; numerous gastro-intestinal diseases; the anorexia of high strung children and young adults, especially young women; and the arteriosclerotic and myocardial degenerations found in the aged. In this group, the mineral deficiencies appear more pronounced than the vitamin deficiencies. As a rule, people with poor appetites have a distaste for meat and milk, and the iron and calcium intake is low. Iron deficiency anemia is almost the rule in such cases. Calcium deficiency is seldom demonstrable either clinically or by blood calcium studies, but very frequently, a brilliant therapeutic response follows large doses of calcium. Vitamin D may possibly help in the utilization of the calcium. Vitamins A, C and D are only too frequently oversupplied, due to the extensive propaganda of those who have something to sell, but even in those patients who do not take concentrated vitamins, I have seldom seen a case of outspoken vitamin deficiency disease in this group. The anorexia itself, the nervous symptoms and the atonic colon which is found so frequently, however, are suggestive evidence of vitamin B deficiency. The normal modern diet is so low in vitamin B that this deficiency should be expected if the diet is limited for any reason. Because of its insidious onset and slow response to treatment, vitamin B should be supplied empirically in large quantities over a long period of time, even though the clinical response does not seem to justify its continued use. Iron, calcium and vitamin B should be considered the

more important potential deficiencies in the diet of the patient with anorexia.

The third group to be considered as potentially subject to deficiency disease is that in which the patients have achlorhydria. If special examinations other than an ordinary test meal are made and a complete achylia gastrica is found, there is all the more reason to suspect the future development of deficiency disease. In such instances, deficient preparation and deficient absorption of the food are both potentially present. Past history would seem to indicate that all clinical conditions which are commonly found in association with achlorhydria should be suspected of being deficiency diseases until they are proved otherwise. It is only necessary to recall the story of pernicious anemia and hypochromic anemia to make this possibility more impressive. Quite a high percentage of patients who have pellagra and sprue also have achlorhydria. May this not mean that many of the disabilities of the last half of life, at which time achlorhydria becomes increasingly prevalent, are due to deficiency? In atrophic or rheumatoid arthritis, a very high incidence of association with achlorhydria and hypochlorhydria is seen, and irrespective of other factors which are involved, the rôle of deficiency disease must not entirely be disregarded as a predisposing factor.

The inference is clear that if achlorhydria is found during an examination, it is important that protection be afforded against future deficiency disease. A careful examination of the blood for microcytosis or macrocytosis may suggest whether it is more important to concentrate on iron or liver therapy. The age and sex of the patient is important. Idiopathic hypochromic anemia practically never develops in the male. Therefore, in males, attention should be concentrated on the protection afforded by liver and vitamin B. Hypochromic anemia is especially prone to develop in young women, and these patients should be urged to take plenty of iron in the diet, and watched carefully to see if large doses of iron should be supplied in other ways. In older women, it is important to supply the extrinsic factor of pernicious anemia and vitamins B_1 and B_2. It is not sufficient to watch these patients for the first signs of pernicious anemia. The value of prophylactic protection was forcibly impressed upon me when I saw two patients recently who had fairly marked subacute and combined degeneration of the spinal cord without any evidence of primary anemia. Both had previously been told that they had achlorhydria and as both improved on liver therapy, I believe it would have been possible to prevent the cord degeneration by prescribing the regular use of liver at the time of finding the achlorhydria. I am happy to say that no responsibility

exists for this unfortunate complication as the achlorhydria had been found in the days when liver was five cents a pound. Today, a physician should not have a very easy conscience if he should fail to advise adequately against the development of such complications. It is true that many patients will not heed the warnings, but that is another problem.

From this viewpoint, a gastric analysis is a highly important routine examination, especially in patients past 40 years of age and the finding of a subacidity or achlorhydria should be the signal to prescribe iron, liver and vitamins B_1 and B_2.

Patients who have chronic liver disease, especially cirrhosis of the liver, will frequently be found to have a macrocytic type of anemia. Some of these patients have achlorhydria, and some do not. In the former, the anemia is due to a lack of absorption and storage of the anti-anemic factor of pernicious anemia. This suggests that such patients should be supplied with this factor, and this should be given by the parenteral method to insure adequate absorption.

Chronic alcoholic addicts must be considered in a special group because they frequently have all the conditions mentioned in the last three groups. As a rule, they eat sparingly, frequently they have an alcoholic gastritis and associated achlorhydria, and in addition, they may have a cirrhotic condition of the liver. It may be years before the latter can be diagnosed clinically by palpating a large liver, but functional impairment of the liver must exist long before this stage is reached. The stage is well set for a deficiency state, and its actual occurrence is not rare as is so well shown by Spies' observation on the relation of pellagra to chronic alcoholism. Alcoholic neuritis is also a deficiency disease.

Chronic alcoholics are frequently seen in every day practice while they are still in a state of good health, but it is important that large quantities of vitamins B_1 and B_2 be given to prevent serious complications, because it is very doubtful if the use of alcohol will be discontinued.

Persistent vomiting from various causes such as neurotic vomiting, vomiting of pregnancy, severe migraine, labyrinthian disease, pyloric obstruction and partial intestinal obstruction is prone to cause such rapid loss of vitamins and minerals that serious deficiency disease results. A state of alkalosis develops from the loss of chlorides, and if this loss is not replaced by large amounts of chlorides by the parenteral groups, the patient rapidly becomes toxic with a high blood carbonate and urea. It is extremely important that the blood chemistry be studied and the alkalosis cleared up, especially before any surgery is attempted

in the obstructive cases. The vomiting in this whole group frequently is persistent only because of the presence of the toxic condition of alkalosis.

Peripheral neuritis is not infrequently seen as a complication of the vomiting of pregnancy. It is possible that, in addition to the loss, an increased demand may be placed on the body during gestation. An adequate supply of vitamin B is indicated and should be given parenterally if the vomiting is severe. Incidentally, iron and calcium should also be supplied liberally to offset anemia, dental decay and other calcium deficiencies. Not only the vomiting of pregnancy, but vomiting from any cause requires the same protection. I have observed two cases of peripheral neuritis due to pyloric obstruction.

The chronic diarrheas act in a similar manner to loss by vomiting, and some diarrheal conditions appear to be due solely to vitamin deficiency. Calcium loss may occur to an extent sufficient to cause rather severe hemorrhagic states. It is very interesting that in one such case which we observed, the calcium was down to 5 mg. per 100 cc., but at no time was tetany observed. The diet is so frequently restricted in fruits that vitamin C should also be watched. As in vomiting, however, lack of vitamins B_1 and B_2 cause the more serious complications and demand more immediate attention.

Extensive resections of the stomach also require special consideration of the anti-anemic factor of pernicious anemia, and the blood should be checked at intervals to determine the need for iron.

In the presence of extensive food allergy where the diet at times is greatly limited, appropriate vitamin protection should be afforded according to the foods which are restricted. Patients on strict diets for obesity, hypertension and nephritis should receive appropriate protection. We observed a very interesting patient at the Cleveland Clinic who had dieted voluntarily because of obesity. A marked edema soon developed which was thought to be due to nephritis. He was treated for this with a strict diet, and the condition became worse. The urinary findings and kidney functional tests did not suggest the presence of nephritis, and he responded immediately to large doses of vitamin B. I have been impressed by the condition of edema of the feet in warm weather which occurs in many stout women who eat lightly, and I have wondered whether it possibly is not a deficiency syndrome.

Many other specific needs for vitamin and mineral protection could be cited, but if the more common conditions mentioned above are kept in mind, the adequate protection of all patients becomes a routine matter. Certain tests have been mentioned that give clues to incipient deficiency states. A gastric analysis should be a routine procedure

in the presence of gastro-intestinal disorders. When an achlorhydria is found, a careful study of the blood for macrocytosis or iron deficiency should be made. Roentgen evidence of dilatation of the colon suggests vitamin B deficiency. Examination of the blood with regard to chlorides, carbon dioxide and urea is indicated when alkaline therapy has been used for a long time. Careful inquiry concerning slight attacks of renal colic may give a clue to the passage of small crystals, and roentgenograms and studies of the urine will give further confirmation.

Clinical symptoms and signs which suggest early deficiency disease should be searched for carefully. Unusual nervous conditions and mild psychic disorders, skin and nail changes, glossitis and atrophic tongue, bleeding gums and dental caries, paresthesias and peripheral pains all suggest early deficiency. Adequate therapy should be given before the more definite deficiency syndromes develop.

The known dangers of hypervitaminosis are relatively rare. I do believe too much vitamin D has been used in the elderly patients with the attendant danger of calcification of the arteries. Vitamins are expensive however, and pharmaceutical houses have specialized on concentrating them and making them attractive and easy to take. Unless there is special need for more than can be supplied naturally in the diet, as in some of the conditions mentioned above, these concentrated expensive products should not replace those in their natural form. Many mild and sometimes severe disorders which complicate gastro-intestinal disease and interfere with treatment are pure deficiency states, and appropriate replacement as outlined above will often be found to be of inestimable value in the solution of very puzzling problems.

From this brief summary of the potential dangers of deficiency disease in the presence of gastro-intestinal disorders, one cannot help but speculate that much can and will be learned about still unrecognized clinical syndromes of deficiency states by a study of the many complicating symptoms and signs that so frequently accompany chronic disease of the gastro-intestinal tract.

In conclusion, I wish to emphasize how important it is to think of disease as possibly resulting from negative agents as well as from positive agents. The only method for combating such diseases is an adequate supply of the missing agent. An even better field for preventive medicine is offered than in diseases due to bacterial origin. In this country where a deficient diet is not common, the prevention of such diseases lies chiefly with those patients who complain of gastro-intestinal disorders.